PUBLIC SUMMARY DOCUMENT
Product: Tamsulosin hydrochloride, prolonged release tablet, 400 micrograms, Flomaxtra®
Sponsor: CSL Biotherapies
Date of PBAC Consideration: March 2008

1. Purpose of Application
The application sought an unrestricted listing for the treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

2. Background
This was the first time tamsulosin had been considered by the PBAC.

3. Registration Status
This formulation of tamsulosin was approved by the TGA as a line extension of the old formulation on 18 January 2006 for the relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

4. Listing Requested and PBAC's View
The submission sought an unrestricted listing.

The PBAC considered a restricted benefit listing would be more appropriate.

5. Clinical Place for the Proposed Therapy
Tamsulosin is used to relieve lower urinary tract symptoms associated with benign prostatic hyperplasia.

6. Comparator
The submission nominated placebo (for no treatment) as the appropriate main comparator.

See Recommendation and Reasons for PBAC's view.

7. Clinical Trials
The submission presented nine randomised trials comparing tamsulosin 4 mg with placebo in men (older than 40 years) with BPH with at least moderate lower urinary tract symptoms (LUTS), using the International Prostate Symptom Score (IPSS) as the outcome of interest in all except one of the trials. That trial uses the Boyarski score.

The trials as published are presented in the following table.

Trial/First author	Protocol title/Publication title	Publication citation
617-CL-307 Chapple CR et al. 2005	Tamsulosin oral controlled absorption system (OCAS) in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH): Efficacy and tolerability in a placebo and active comparator controlled phase 3a study.	European Urology Supplements 4:33-44.
617-CL-303 Chapple CR, et al. 2005	Tamsulosin oral controlled absorption system (OCAS) in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH): Efficacy and tolerability in a phase 2b dose-response study.	European Urology Supplements 4:25-32.

91HAR02 and 91HAR01 Meta-analysis Chapple CR, et al 1996	Tamsulosin, the first prostate-selective alpha 1Aadrenoceptor antagonist. A meta-analysis of two randomized, placebo-controlled, multicentre studies in patients with benign prostatic obstruction (symptomatic BPH).	European Tamsulosin Study Group. European Urology 29:155-167.
Chapple CR, et al. 1997	Tamsulosin 0.4 mg once daily: tolerability in older and younger patients with lower urinary tract symptoms suggestive of benign prostatic obstruction (symptomatic BPH).	The European Tamsulosin Study Group. European Urology 32:462-470.
Abrams P, et al 1995	Tamsulosin, a selective alpha 1c-adrenoceptor antagonist: a randomized, controlled trial in patients with benign prostatic 'obstruction' (symptomatic BPH).	The European Tamsulosin Study Group. British Journal of Urology 76:325-336.
92-03A 92-03B extension Lepor H. 1998b	Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia.	Tamsulosin Investigator Group. Urology 51:892-900
Lepor H. 1998a	Long-term evaluation of tamsulosin in benign prostatic hyperplasia: placebo-controlled, double-blind extension of phase III trial.	Tamsulosin Investigator Group. Urology 51:901-906
93-01 Narayan P et al 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. Journal of Urology 160:1701-1706.
Narayan P et al 2000	A comparison of two phase III multicenter, placebo-controlled studies of tamsulosin in BPH	Advances in Therapy 2000
Kaplan et al, 2006	Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial.	JAMA 296:2319-28
Djavan et al, 2005	The impact of tamsulosin oral controlled absorption system (OCAS) on nocturia and the quality of sleep: Preliminary results of a pilot study.	European Urology Supplements 4:61-68.
Nordling. 2005	Efficacy and safety of two doses (10 and 15 mg) of alfuzosin or tamsulosin (0.4 mg) once daily for treating symptomatic benign prostatic hyperplasia.	BJU International 95:1006-1012.
Mohanty et al, 2003	A double blind placebo controlled study of tamsulosin in the management of benign prostatic hyperplasia in an Indian population.	Annals of the College of Surgeons of Hong Kong 7:88-93.

8. Results of Trials

The key results are summarised in the table below.

Results of change in prostate symptom scores from baseline to endpoint in the direct trials

Trial ID	Tamsulosin		Placebo		Mean difference (95% CI)
	End point (SD)	Change (SD)	End point (SD)	Change (SD)	
International Prostate Symptom Score					
617-CL-307 OCAS	10.8 (6.2)	-7.7 (5.8)	12.4 (6.4)	-5.8 (5.6)	-1.9 *(-2.8, -1.0)*
617-CL-307 MR	10.6 (5.9)	-8.0 (5.6)	12.4 (6.4)	-5.8 (5.6)	*-2.2 (-3.0, -1.5)*
617-CL-303	10.4 (5.5)	-7.6 (5.3)	11.7 (6.1)	-6.0 (5.4)	-1.6 *(-2.6, -0.6)*
92-03A	11.5	-8.3 (6.3)	14.1	-5.5 (6.3)	-2.8 *(-3.9, -1.7)*
93-01	12.8	-5.1 (6.4)	15.6	-3.6 (5.7)	-1.5 *(-2.6, -0.4)*
Djavan 2005	10.2	-8.0 (5.2)	12.5	-5.6 (4.7)	-2.4 *(-4.2, -0.6)*
Nordling 2005	10.9	-6.5 (6.2)	13.1	-4.6 (5.8)	-1.9 *(-3.3, -0.5)*
Mohanty 2003	6.9 (4.4)	-12.6	12.7 (4.0)	-5.8	-6.8
Boyarski score					
	6.1 (3.2)	-3.3 (3.1)	7.0 (3.4)	-2.4 (3.2)	-0.9 *(-1.4, -0.4)*
Pooled analysis *(excluding Mohanty 2003 and 91 HAR 02/ 91 HAR 01)*					
Pooled relative risk (random effects)					-2.02 (-2.41, -1.63)
Chi-square for heterogeneity: P= *I^2 statistic with 95% uncertainty interval =*					*0.69* *0%*

Although all the placebo-controlled trials showed a statistically significant improvement in IPSS, the incremental benefit of approximately 2 points over placebo achieved with tamsulosin therapy was small, and its clinical importance was considered uncertain. The PBAC noted the strong placebo response in the clinical trials. A 14.9% change in symptom score occurred with placebo, and only an extra 5.8% change occurred with tamsulosin treatment. It also appears that the majority of the clinical benefit is observed within the first 4 weeks of therapy.

Quality of life data were not discussed in the submission and were difficult to find in some of the individual study reports. The Pre-Sub Committee response provided additional information and argued that the majority of results showed a significant benefit for tamsulosin over placebo. The PBAC noted that, in general, measures of quality of life, other than the 'bother' score tended not to reach statistical significance.

There were statistically significant increases in treatment related adverse events compared with placebo (RR 1.39 [95% CI 1.09, 1.78]), and the major adverse events were problems with ejaculation, with statistically significant increases in relative risk in all trials except one, and a pooled relative risk of 6.79 (95% CI 3.29, 14.00). There was a small statistically significant effect on hemodynamics with tamsulosin treatment.

Intraoperative Floppy Iris Syndrome (IFIS) was observed during cataract surgery in some patients treated with alpha-1 blockers including tamsulosin, and priapism is a rare but serious adverse effect.

9. Clinical Claim

The submission described tamsulosin as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo.

For PBAC's views see Recommendation and Reasons.

10. Economic Analysis

The submission presented a trial-based economic evaluation based on direct randomised trials of tamsulosin (12 weeks duration) and a modelled evaluation representing chronic therapy (12 months). The type of economic evaluation presented was a cost-utility analysis. It was a simple model that applied the drug and GP costs and utility associated with symptom improvement to tamsulosin- and placebo-treated patients. The time horizon was 12 months.

The trial based incremental cost per Quality-Adjusted Life-Year (QALY) gained as 12 weeks was estimated in the submission to be between $45,000 and $75,000. The modelled incremental cost per QALY gained over 12 months was estimated in the range of $15,000 to $45,000.

The PBAC noted:

- the simple structure and short time horizon of the model did not allow for costs and health outcomes associated with treatment-related adverse events, episodes of acute urinary retention avoided or surgery delayed or avoided.
- the economic model was sensitive to the assumptions made in the QALY estimates, both in the methods used to derive the utilities and the extrapolation of utilities past the duration of the trial data.

For PBAC's views see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The cost per year to the PBS was estimated in the submission to be in the range of $30 to $60 million in Year 5.

12. Recommendation and Reasons

The PBAC considered that a restricted benefit listing might be more appropriate than the unrestricted listing proposed in the submission.

The PBAC considered that the choice of placebo as the only comparator in the submission was not appropriate. Prazosin is the most commonly prescribed therapy for the treatment of benign prostate hyperplasia (BPH) and the only one currently listed on the PBS, and is therefore a relevant comparator. The PBAC noted the submission's argument that prazosin is not recommended as a treatment for LUTS in management guidelines for BPH. However, the choice of comparator in submissions to the PBAC is not determined by whether a therapy is recommended or not by therapeutic guidelines, but by whether that therapy is the one most likely to be replaced in Australian clinical practice should tamsulosin be listed on the PBS. According to the definition of the main comparator in the PBAC guidelines, the therapies most likely to be replaced in clinical practice, should tamsulosin become available on the PBS, would be prazosin, and in addition, to account for a proportion of patients who may currently be untreated, placebo.

The submission used symptom scores measured by the International Prostate Symptom Score (IPSS) and the Boyarski score, as primary outcome, and maximal urinary flow rate as a secondary outcome. The IPSS consists of 7 items (4 obstructive symptom items and 3 irritative symptoms items), totalling a maximum of 35 points. A total score of 0-7 points is suggestive of mild disease, a score of 8-19 moderate disease, and 20-35 severe disease. The PBAC noted that the IPSS is a standard tool to measure LUTS and is used as a clinical tool as

well as a research measure. However, the PBAC was concerned that no clinically important relationship between the total IPSS, prostate size, urinary flow and obstruction had been demonstrated. In addition, the natural history of untreated BPH is variable, making validation problematic.

Although all the placebo-controlled trials showed a statistically significant improvement in IPSS, the incremental benefit of approximately 2 points over placebo achieved with tamsulosin therapy was small, and its clinical importance was considered uncertain. The PBAC noted the strong placebo response in the clinical trials. A 14.9% change in symptom score occurred with placebo, and only an extra 5.8% change occurred with tamsulosin treatment. It also appears that the majority of the clinical benefit is observed within the first 4 weeks of therapy. The PBAC also considered that the extent of the quality of life gains achieved with tamsulosin therapy were uncertain and mainly related to "bother" scores.

The PBAC noted the statistically significant increases in treatment related adverse events compared with placebo, mainly abnormal ejaculation, and intraoperative floppy iris syndrome in some patients undergoing cataract surgery. Tamsulosin therapy resulted in small, and unlikely to be clinically important, reduction in blood pressure, and no statistically significant decrease in heart rate.

The PBAC considered that the trial-based incremental cost-effectiveness ratio of between $45,000 and $75,000 per extra QALY gained at 12 weeks and modelled incremental cost-effectiveness ratio of between $15,000 and $45,000 per extra QALY gained over 12 months to be unacceptably high and uncertain because the results are very sensitive to the utility estimates used. In addition, the utility estimates did not take into account treatment-related adverse events. The modelled economic evaluation also assumed that the effect of the mean change from baseline to endpoint (12 weeks) continues for 12 months. The assumption was based on trial 92-03B, a 40-week double-blind extension of trial 92-03A, and an open-label three-year follow-up study of patients enrolled in trials 91 HAR 02/01. Only limited comparative efficacy data are available from these studies. Of note are the large discontinuation rates observed in the 3-year open-label study (21% at week 48 and 48% at week 108) which were mainly related to lack of efficacy.

The PBAC also noted the large additional PBS expenditure of between $30 and $60 million in the first five years should tamsulosin be subsidised.

The PBAC therefore rejected the submission because of unacceptably high and uncertain cost-effectiveness ratios.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor has since consulted with the PBAC and the Department of Health and Ageing to clarify the reasons for rejection and will consider addressing them in a re-submission.