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

1. Purpose of Application
The submission sought a restricted benefit listing for the treatment of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).

2. Background
The PBAC had considered tamsulosin for PBS listing on one previous occasion. At its March 2008 meeting, the PBAC considered a submission for tamsulosin seeking an unrestricted benefit for LUTS associated with BPH. The PBAC rejected the submission because of high and uncertain cost-effectiveness ratios. (See also Public Summary Document of March 2008).

Tamsulosin has been available as a private prescription since it was registered with the TGA in 1999 as a modified release capsule under the tradename Flomax®. A prolonged release oral controlled absorption system tablet formulation of tamsulosin was registered by the TGA on 18 January 2006 under the tradename Flomaxtra®.

3. Registration Status
This formulation of tamsulosin was approved by the TGA as a line extension on 18 January 2006 for the relief of LUTS associated with BPH.

4. Listing Requested and PBAC's View
Restricted benefit
Lower urinary tract symptoms due to benign prostatic hyperplasia.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
LUTS due to BPH includes symptoms such as hesitancy, dribbling after urination, nocturia, frequency and urgency and may culminate in urinary retention. Tamsulosin is used to relieve LUTS due to BPH.

6. Comparator
The submission nominated prazosin and placebo as the main comparators. This was as previously advised by the PBAC.

7. Clinical Trials
No changes had been made to the trial data presented in the previous submission. (See list of published trials in Public Summary Document of March 2008).

8. Results of Trials
There was a statistically significant reduction in the international prostate symptom score (IPSS) following treatment with tamsulosin compared to placebo (pooled mean difference -2.0, 95 % CI: -2.4, -1.6). However, the clinical significance of this result was uncertain.

The re-submission did not present an indirect comparison of tamsulosin versus prazosin although prazosin was presented as a comparator. During the evaluation a prazosin versus placebo study (Steven et al 1993) was located which examined the IPSS score, hence an indirect comparison of tamsulosin versus prazosin in terms of IPSS score could be performed. The indirect comparison of tamsulosin versus prazosin estimated a non-significant difference in the mean difference in IPSS score at 12 weeks (weighted mean difference =-1.22, 95 % CI: -2.67, 0.23).

Also located during the evaluation were two 12-week studies of prazosin versus placebo (Chapple et al 1992; 1990) examining maximal urine flow rate (Qmax), hence an indirect comparison of tamsulosin versus prazosin using the outcome of Qmax was also conducted. An indirect comparison of tamsulosin versus prazosin using the change in Qmax from baseline to 12 weeks as the outcome demonstrated a statistically significant difference between tamsulosin and prazosin favouring prazosin weighted mean difference of -1.56 (95 % CI: -2.94, -0.18).

No new toxicity data were presented in the re-submission. The key results are summarised below.

There were statistically significant increases in treatment related adverse events for tamsulosin 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 haemodynamics with tamsulosin treatment, but this was unlikely to be of clinical importance. Intraoperative Floppy Iris Syndrome (IFIS) had been observed during cataract surgery in some patients treated with alpha-1 blockers including tamsulosin, and priapism. This was a rare but serious adverse effect.

The common adverse effects with prazosin were orthostatic hypotension and dizziness.

9. Clinical Claim

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

The re-submission implicitly claimed that tamsulosin was non-inferior to prazosin in accepting the price of prazosin for the proportion of prazosin patients switching to tamsulosin. The indirect comparison of tamsulosin versus prazosin performed during the evaluation demonstrated that tamsulosin was non-inferior to prazosin in terms of IPSS score, however the possibility that tamsulosin was inferior to prazosin could not be excluded when considering the outcome of maximum urine flow rate (Qmax). As noted for the change in IPSS score, the clinical significance of the change in Qmax was also uncertain.

10. Economic Analysis

An updated modelled economic evaluation was presented. The proposed price reduction for tamsulosin was applied in the updated economic evaluation in the re-submission. The re-submission did not formally compare the costs and effects of tamsulosin and prazosin in its modelled economic evaluation.

The structure and all inputs to the model used in the March 2008 submission remained unchanged.

The incremental cost per Quality Adjusted Life Year (QALY) gained was $45,000 - $75,000, based on the trial duration of 12 weeks. The incremental cost per QALY gained was $15,000 – $45,000, based on costs and QALYs over 12 months (assuming the utility differences at 12 weeks are maintained to 52 weeks).

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be in the range of 100,000–200,000, while the likely financial cost per year to the PBS (minus any savings in use of other drugs) was estimated to be up to $10-30 million ($30–60 million using prices updated for the 1 August 2008 PBS pharmacy dispensing fees and mark-ups) in Year 5.

12. Recommendation and Reasons

The PBAC accepted that the resubmission requested listing for a suitable restricted benefit listing compared to the previous request for unrestricted listing. The PBAC also confirmed its March 2008 advice that the two main comparators in this population were placebo for no PBS-subsidised medicine and prazosin, accepted the projected substitution rates for these two comparators in the resubmission and noted the related price reduction.

The placebo-controlled randomised trials provided data in relevant populations. They reported small clinical benefits over placebo (a meta-analysed mean difference in the International Prostate Symptom Score (IPSS) of -2.0 (95 % CI: -2.4, -1.6) from baselines of around 19 on a 35-point scale. The PBAC accepted that this difference was clinically important for patients, but that the nature of the 2-point difference might vary in importance depending on which of the seven items (e.g. irritation, nocturia, dribbling) were favourably affected in any single patient. The difference was sustained over 40 weeks in one trial. The mean difference in total maximal urine flow rate (Qmax) was also statistically significantly improved with tamsulosin over placebo, but the clinical importance of this secondary outcome was more difficult to interpret. The PBAC noted useful input from both clinicians and patients in interpreting the evidence on effectiveness. Tamsulosin and prazosin results were similar for the IPSS across the indirect comparison involving placebo as the common reference, but these were not formally analysed to assess non-inferiority. The Qmax results appeared to have statistically significantly favoured prazosin over tamsulosin, but the PBAC accepted that this might not be a real difference due to differences across the compared trials.

Tamsulosin was generally well tolerated with increased risk of ejaculation problems, priapism and increased risk during cataract surgery compared to placebo. Prazosin caused more postural hypotension (important in the prevalent population), headache and tachycardia.

The PBAC noted the price reduction compared to the previous submission, but considered that the modelled economic evaluation resulted in an unacceptably high and uncertain incremental cost-utility ratio for the requested listing. In particular, the translation into utilities (a mean incremental QALY gain of 0.0113 per patient per year, which was unchanged from the previous submission) remained uncertain.

The PBAC noted a substantial private market had developed for medicines to treat this condition, which was relevant to the estimate of uptake of any medicine specifically listed on

the PBS for these patients. The PBAC decided not to recommend listing on the basis of unacceptable and uncertain cost-effectiveness.

Recommendation: ***Reject***

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

CSL is very disappointed with the PBAC's rejection of this 2nd submission seeking listing of tamsulosin and that tamsulosin cannot be made available on the PBS for sufferers of LUTS associated with BPH at this time.