**PUBLIC SUMMARY DOCUMENT**
**Product:** Dutasteride, capsule, 0.5 mg, Avodart®
**Sponsor:** GlaxoSmithKline Australia Pty Ltd
**Date of PBAC Consideration: July 2009**

## 1. Purpose of Submission
The submission sought an Authority required (Streamlined) listing for the treatment of benign prostatic hyperplasia (BPH) in men over 50 years who meet certain criteria.

## 2. Background
This drug had not previously been considered by the PBAC.

## 3. Registration Status
Dutasteride was TGA registered on 14 November 2002 for the treatment of patients with symptomatic benign prostatic hyperplasia with an enlarged prostate.

## 4. Listing Requested and PBAC's View
Authority required (STREAMLINED)
In combination with an alpha-blocker, treatment of benign prostatic hyperplasia in men aged 50 years and over with an International Prostate Symptom Score (IPSS) > 7 and a prostate specific antigen level ≥ 1.5 ng/mL.

NOTE:
The IPSS is publicly available online at:
http://www.usrf.org/questionaires/AUA SymptomScore.html
Prostate specific antigen testing is subsidised through Medicare

During the review the sponsor suggested that the IPSS requirement could be amended to address any concerns the PBAC may have had with the severity of lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH) in the trial population being more severe than the proposed restriction.

*For PBAC's views see Recommendation and Reasons.*

## 5. Clinical place for the proposed therapy:
When mild symptoms of BPH can no longer be managed by 'watchful waiting', current treatment options for patients with moderate to severe symptoms include treatment with an alpha antagonist (eg. prazosin, tamsulosin, terazosin) and/or a 5 alpha reductase inhibitor (eg. finasteride, dutasteride) or surgery.

## 6. Comparator
The submission nominated monotherapy with prazosin hydrochloride as the main comparator.

## *7.* Clinical trials
The submission presented one randomised trial comparing dutasteride + tamsulosin with tamsulosin monotherapy in male patients with moderate to severe BPH aged ≥50 years. There were no trials identified comparing dutasteride + prazosin with prazosin

monotherapy, which was the main comparator nominated by the submission. The submission assumed the efficacy and safety of tamsulosin to be no different to other alpha blockers, such as prazosin.

Publication details of the trial presented are shown below:

| Trial ID/First Author | Protocol title/ Publication title | Publication citation |
|---|---|---|
| **Direct randomised trial** | | |
| ARI40005 | The effects of dutasteride and tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the ComBAT Study | Roehrborn CG, Siami P, Barkin J, et al (2008). *The Journal of Urology*; 179 :616-21 |

The PBAC noted tamsulosin is not available on the PBS, and has not been deemed cost effective in comparison with prazosin when previously considered by the PBAC.

## 8. Results of trials

The primary outcome of the trial was adjusted mean difference in IPSS scores at 24 months between patients treated with dutasteride +tamsulosin and tamsulosin monotherapy. The results illustrate that combination treatment with dutasteride/tamsulosin gave statistically greater improvement in IPSS scores over tamsulosin monotherapy at two years, mean difference -1.8. No statistically significant difference in IPSS was detected between combination therapy and tamsulosin monotherapy prior to 9 months of treatment.

The PBAC noted the adverse events (AEs) profiles of dutasteride and tamsulosin are relatively well established. In trial ARI40005 at the two years analysis time point, the overall incidence of AEs and serious adverse events (SAEs) was similar across the treatment groups (any AEs: combination: 65% tamsulosin: 63%, dutasteride: 64%); SAE, combination 12% vs tamsulosin 13%, dutasteride: 12%). The numbers of AEs leading to treatment discontinuations were similar between combination and tamsulosin treated patients.

## 9. Clinical Claim

The submission described dutasteride/alpha-blocker combination treatment as superior in terms of comparative effectiveness and inferior in terms of comparative safety over alpha blocker alone.

*For PBAC's views see Recommendation and Reasons.*

## 10. Economic Analysis

A stepped economic evaluation was presented. The economic evaluation compared treatment costs and outcomes over a 10 year time horizon for BPH patients treated with:

- Combination therapy with dutasteride (0.5mg) daily and prazosin (2mg) twice daily
- Monotherapy with prazosin (2 mg) twice daily

Both alternatives represented chronic therapy, which was assumed to be continued until the earlier of treatment withdrawal, surgery or death.

The calculation method employed was a cohort/expected value approach. No Monte Carlo simulation had been used to represent either patient variation or parameter uncertainty. The economic evaluation included five health states and two transitional events.

The submission estimated dutasteride/prazosin combination treatment is associated with a cost/QALY of between $15000 - $45000 when compared with prazosin treatment alone. The model was most sensitive to changes in BPH severity utility.

## 11. Estimated PBS Usage and Financial Implications

The financial cost/year to the PBS was estimated to be up to $10-30m in Year 5.

## 12. Recommendation and Reasons

The PBAC considered the proposed restriction did not correlate with the severity of lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH) in the trial population given the entry criteria for the trial included an international prostate symptom score (IPSS) of greater than or equal to 12 representing more severe symptoms than the original proposed restriction IPSS of greater than or equal to seven. The PBAC considered that IPSS was not an appropriate measure for use in general practice, and it is not specific for assessing LUTS due to prostatic hyperplasia, as it does not distinguish the effects of prostatic hyperplasia from the effects of bladder detrusor muscle overactivity, which may co-exist or occur separately.

The PBAC noted the mean prostate specific antigen (PSA) test result in the trial population was 4.0 ng/mL and the PSA in the requested restriction was greater than or equal to 1.5 ng/mL. The PBAC also considered it was not appropriate to limit the restriction to those aged 50 and over.

The PBAC considered the comparator of prazosin monotherapy appropriate, however the assumption in the submission that tamsulosin is of equal efficacy and safety to prazosin was considered uncertain. Additionally tamsulosin was not available on the PBS.

Trial ARI40005 comparing the effectiveness of tamsulosin with dutasteride to tamsulosin alone showed a mean difference of 1.8 in IPSS score from baseline for the combination compared to tamsulosin alone at 24 months. Although this is a statistically significant change, the PBAC considered the improvement in IPSS small and of uncertain clinical significance. The PBAC considered the change of 1.8 in IPSS may have clinical meaning for some patients depending on which of the items assessed in the IPSS have improved and the severity of the patient's LUTS. The PBAC also noted that no statistical difference in IPSS was evident between the combination and tamsulosin alone prior to nine months of treatment and hence in practice patients would need to take the combination continuously for a substantial period of time before determining if the individual was benefiting from the combination treatment.

The combination treatment with tamsulosin and dutasteride was considered to be generally consistent with the known safety profile of the individual monotherapies. At the two year analysis time point in ARI40005 the overall incidence of adverse events,

including serious adverse events, was similar in the combination group to tamsulosin and dutasteride alone.

A stepped economic evaluation was presented in the submission comparing treatment costs and outcomes of combination therapy with dutasteride 0.5 mg and prazosin 2 mg with prazosin 2 mg monotherapy over a ten year time horizon. Five health states of mild BPH (IPSS less than or equal to seven), moderate BPH (IPSS between eight and 19 inclusive), severe BPH (IPSS greater than or equal to 20), post transurethral resection of the prostate (TURP), and death (all cause mortality) and two transition states of acute urinary retention and TURP were included in the model. In the model, once the patient had undergone a TURP, it was assumed the patient received no further medical management of LUTS associated with BPH. The PBAC considered this was not appropriate as patients may receive medical treatment after they have undergone a TURP. The PBAC considered the incremental cost per quality adjusted life year of combination treatment with dutasteride and prazosin versus prazosin alone derived from the model of between $15,000 and $45,000 to be highly uncertain.

The PBAC considered there was uncertainty associated with the utilities applied to the health states in the model and that there was insufficient examination of the sensitivity of the utility estimates.

The utilisation of dutasteride is likely to be higher than that estimated in the submission when taking into account inclusion of patients under the age of 50 years.

The PBAC rejected the submission on the basis of uncertain clinical benefit and highly uncertain cost effectiveness stemming from the clinical uncertainty and uncertainty in the utilities applied to the health states in the economic model. The PBAC was also concerned regarding the practical implementation of the restriction which by its nature is linked to the economic model.

***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

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