PUBLIC SUMMARY DOCUMENT
Product: Dutasteride, capsule, 500 micrograms, Avodart®
Sponsor: GlaxoSmithKline Australia Pty Ltd
Date of PBAC Consideration: November 2009

1. Purpose of Application

The submission sought an Authority Required (STREAMLINED) listing for the treatment, in combination with an alpha-antagonist, of lower urinary tract symptoms due to benign prostatic hyperplasia (BPH) where treatment has been initiated by a urologist.

2. Background

At the July 2009 meeting, the PBAC rejected a submission seeking an Authority Required (STREAMLINED) listing for the treatment of benign prostatic hyperplasia in men over 50 years who meet certain criteria 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.

For further details see the relevant Public Summary Document for the meeting.

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)
Treatment, in combination with an alpha-antagonist, of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) where treatment has been initiated by an urologist.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Benign prostatic hyperplasia (BPH) is a typically progressive condition associated with worsening lower urinary tract symptoms such as hesitant and interrupted weak stream, urgency, leaking or dribbling and a sense of incomplete voiding leading to more frequent urination, especially at night. The condition may eventually require surgery.

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.

Dutasteride would provide an alternative treatment for BPH.

6. Comparator

As previously, the submission nominated monotherapy with prazosin hydrochloride as the main comparator. This was considered appropriate by the PBAC at the July 2009 meeting.

7. Clinical Trials

The re-submission addressed the following issues, which were raised at the July 2009 PBAC meeting:

- The requirement for International Prostate Symptom Score (IPPS) and Prostate Specific Antigen (PSA) in the restriction
- The relative efficacy and safety of tamsulosin and prazosin
- Sensitivity of the economic evaluation to the utilities of the individual health states
- Likely underestimation of the utilities

The submission identified the following references in support of its request for listing.

Trial ID/ First Author	Protocol title/Publication title	Citation
Baladi JF, et al (1996)	An economic evaluation of finasteride for treatment of benign prostatic hyperplasia.	Pharmacoeconomics; 9(5): 443-454
Bar-Yosef Y, et al (2008)	Alpha blockers in use for symptomatic benign prostatic hyperplasia--are all drugs born equal?	Harefuah; 147(6): 514-519
Berges R, et al (2003)	Impact of therapy used in clinical practice on lower urinary tract symptoms/benign prostatic hyperplasia (LUTS/BPH) disease progression.	European Urology Supplements; 2: 19-24.
Cowles RS et al (1995)	A prospective randomized comparison of transurethral resection to visual laser ablation of the prostate for the treatment of benign prostatic hyperplasia.	Urology; 46(2): 155-60.
DiSantostefano RL, et al (2006).	The long-term cost effectiveness of treatments for benign prostatic hyperplasia.	Pharmacoeconomics; 24(2): 171-191.
Djavan B, et al (2004).	State of the art on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia.	Urology; 64: 1081-1088.
Djavan B, et al (1999).	A meta-analysis on the efficacy and tolerability of á1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction.	European Urology; 36: 1-13.
Donovan JL, et al (2000).	A randomized trial comparing transurethral resection of the prostate, laser therapy and conservative treatment of men with symptoms associated with benign prostatic enlargement: the CLasP study.	The Journal of Urology; 164: 65-70.
Hill B, et al (2004).	Transurethral needle ablation versus transurethral resection of the prostate for the treatment of symptomatic benign prostatic hyperplasia: 5-year results of a prospective, randomized, multicenter clinical trial.	The Journal of Urology; 171: 2336-40.
Kortmann BB, et al (2002).	Urodynamic effects of alpha-adrenoceptor blockers: a review of clinical trials.	Urology; 62: 1-9.
MacDonagh RP, et al (1997).	The use of generic measures of health-related quality of life in the assessment of outcome from transurethral resection of the prostate.	British Journal of Urology; 79: 401-408.

Noble SM, et al (2002).	Transurethral prostate resection, noncontact laser therapy or conservative management in men with symptoms of benign prostatic enlargement? An economic evaluation.	The Journal of Urology; 168: 2476-2482.
Roehrborn CG, et al (1999).	The effects of transurethral needle ablation and resection of the prostate on pressure flow urodynamics parameters: analysis of the United States randomized study.	The Journal of Urology; 162: 92-7.
Trueman P, et al (1999).	Prevalence of lower urinary tract symptoms and self-reported diagnosed 'benign prostatic hyperplasia', and their effect on quality of life in a community-based survey of men in the UK.	BJU International; 83: 410-415.

8. Results of Trials

The following table shows the 48 month data from the ARI40005 (Roehrborn 2008) trial together with the 24 month data which was used in the previous submission.

Baseline, endpoint, change from baseline and adjusted mean difference in International Prostate Symptom Score (IPSS) scores at 24 and 48 months (ITT population)

Timepoint	Endpoint	Dutasteride + Tamsulosin	Tamsulosin	Mean difference
Baseline	Mean IPSS (SD)	16.6 (6.35)	16.4 (6.10)	
24 months	Mean IPSS [SE]	10.1 [0.16]	11.9 [0.17]	
	Adjusted Mean Change from baseline [SE]	-6.2 [0.15]	-4.3 [0.15]	-1.8 p<0.001
48 months	Adjusted Mean Change from baseline	-6.3	-3.8	-2.5 p<0.001

The data showed a greater change in the adjusted mean difference in IPSS from baseline at 48 months than at 24 months.

The table below summarises the acute urinary retention (AUR) and BPH surgery rates from ARI40005.

AUR and BPH surgery rates from ARI40005

	Dutasteride + Tamsulosin		Tamsulosin	
	No. Events	No. persons at risk	No. Events	No. persons at risk
BPH-surgery	38	1610	126	1611
Risk reduction	70.6% (57.7%, 79.5%)			
AUR	36	1610	109	1611
Risk reduction	67.6% (52.7%, 77.8%)			

Regarding the comparison between tamsulosin and prazosin, the PBAC previously considered that the assumption that tamsulosin is of equal efficacy and safety to prazosin was uncertain. The Pre-PBAC Response acknowledged that there may be some uncertainty in the relative efficacy of tamsulosin and prazosin. However, the incremental difference in BPH

symptoms between combination treatment and alpha-antagonist monotherapy was unlikely to be significantly affected based on the alpha-blocker used.

The withdrawal rates from treatment were updated and at 48 months 69% of the dutasteride plus tamsulosin group remained on treatment compared to 61% of the tamsulosin only group. summarised in the table below.

For PBAC's view see Recommendation and Reasons.

9. Clinical Claim

As previously, the submission claimed dutasteride/alpha-blocker combination treatment to be superior in terms of comparative effectiveness and inferior in terms of comparative safety over alpha blocker alone.

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

The submission presented a Markov model running for 10 years with a cycle length of 3 months. The structure of the model was unchanged from the previous submission. A new base cost-effectiveness ratio was calculated.

The effect of all the changes to the inputs of the model lowered the cost per QALY compared to the previous submission though it remained between $15,000 to $45,000.

The submission conducted a number of sensitivity analyses varying the utility values of the health states. The majority of the results from the sensitivity analyses were between $15,000 - $45,000.

For PBAC's view see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The estimates were recalculated in this submission and include men aged 40 years and older. This submission assumed the same proportion of men aged between 40 and 50 years will have moderate or severe BPH as the 18 – 50 year old age group. The submission estimated between 100,000 – 200,000 men are likely to be on combination therapy by year 5 of listing.

The incremental cost to the Government was estimated to be less than $10 million by year 5 of listing.

12. Recommendation and Reasons

The PBAC recommended the listing of dutasteride on the PBS as an authority required (streamlined) benefit for the treatment, in combination with an alpha-antagonist, of lower urinary tract symptoms due to benign prostatic hyperplasia (BPH), where treatment is initiated by a urologist, on the basis of acceptable cost effectiveness compared with alfa-antagonist alone.

The PBAC considered the removal from the revised restriction of IPSS, prostate specific antigen level and limitation to men aged 50 years and over appropriate. The PBAC also considered restriction to initiation by a urologist appropriate, noting that mild BPH patients

were removed from the baseline in the economic model on the basis that it is unlikely that urologists would be treating mild BPH with the combination of dutasteride and an alpha-antagonist.

The PBAC noted that the re-submission included four year data from trial ARI40005, and that the economic model was updated with the four year data. The key data provided by the updated trial analysis are the reduction in AUR and BPH surgery needed by patients treated with dutasteride in comparison with the alpha-antagonist alone. At 48 months the mean difference in International Prostate Symptom Score (IPSS) was 2.5 points from baseline for dutasteride in combination with tamsulosin compared to tamsulosin alone. The acute urinary retention (AUR) rate at 48 months with combination therapy compared to tamsulosin alone showed a risk reduction of 67.6 % (CI: 52.7 %, 77.8 %), and the risk reduction for BPH surgery was 70.6 % (CI: 57.7%, 79.5%).

Updates to the economic model included the removal of mild BPH patients at baseline and changed proportions of patients with mild, moderate and severe BPH health states, updated year three and four BPH transition probabilities, inclusion of four year AUR and BPH-surgery rate data from ARI40005, updated withdrawal rates from ARI40005 four year data, updated adverse event rates from ARI40005 four year data, inclusion of an assumption that patients will continue medical treatment of BPH post BPH-surgery, and amendment of the cost of BPH-surgery. This resulted in a new base case incremental cost effectiveness ratio of between $15,000 – $45,000 per QALY gained. The PBAC noted that of the four year data on AUR and BPH-surgery rates replaced the estimates used in the previous submission derived from McConnell et al 2003 and considered the application of the trial rates to the economic model reduced the uncertainty in the economic modelling.

The PBAC considered that uncertainty in relation to the variable sources of utilities remained, despite the further sensitivity analysis conducted in the re-submission. The sensitivity analysis in the re-submission was extended to allow for a wider range of differences between mild, moderate and severe BHP. Nevertheless, the sensitivity analyses indicated that the incremental cost effectiveness ratios remained in an acceptable range.

The PBAC noted that the re-submission utilisation estimates were increased to include men aged 40 years and older. The PBAC considered uncertainty remained with the utilisation estimates.

On balance the PBAC concluded that the four year data from trial ARI40005 provided in the re-submission and incorporated in the economic model reduced the clinical and economic uncertainty and the ICER of between $15,000 – $45,000 was acceptable.

Recommendation:
DUTASTERIDE, capsule, 0.5 mg

Restriction:	Authority Required (STREAMLINED) Treatment, in combination with an alpha-antagonist, of lower urinary tract symptoms due to benign prostatic hyperplasia where treatment is initiated by a urologist.

Maximum quantity: 30
Repeats: 5

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

GlaxoSmithKline Australia welcomes the positive recommendation of the PBAC and looks forward to finalising the listing of dutasteride on the PBS for the treatment of benign prostatic hyperplasia.