PUBLIC SUMMARY DOCUMENT

Product: Solifenacin succinate, tablet, 5 mg & 10 mg, Vesicare®

Sponsor: Arrow Pharmaceuticals Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission sought a restricted benefit PBS listing for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency or increased urinary frequency in patients where treatment with oxybutynin has failed or is not tolerated.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Solifenacin was TGA registered on 28 August 2006 for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency or increased urinary frequency.

4. Listing Requested and PBAC's View

Restricted benefit

Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency or increased frequency in patients where treatment with oxybutynin has failed or is not tolerated.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

People who suffer from Overactive Bladder Syndrome (OAB) experience an unpredictable urgent need to empty the bladder, that may involve urinary leakage some or all of the time. The syndrome can impact on a person's ability to complete their daily activities, and reduce their quality of life.

Solifenacin is a treatment option for this condition.

6. Comparator

The submission nominated placebo for standard medical management as the main comparator.

The PBAC accepted that placebo for standard medical management would be an appropriate comparator if solifenacin is used only in the population for whom listing is sought. However, as there is a substantial risk of utilisation beyond the restriction, oxybutynin may also be an appropriate comparator. Tolterodine, although currently not listed on the PBS, may also be an appropriate comparator.

7. Clinical Trials

The submission presented a series of meta-analyses based on the results of eight head-to-head randomised comparative trials comparing solifenacin (5 mg & 10 mg daily) and placebo in patients with overactive bladder.

The submission also presented three randomised head-to-head trials comparing solifenacin (5 mg & 10 mg daily) and tolterodine (4 mg daily) in patients with overactive bladder.

No trial evidence was presented specifically for patients who have failed or are intolerant to oxybutynin.

The studies published at the time of submission are as follows:

Trial/First author	Protocol title/Publication title	Publication citation
Key trials (solifenacin versus placebo)		
905-CL-005 Chapple CR et al, 2004	Solifenacin appears effective and well tolerated in patients with symptomatic idiopathic detrusor overactivity in a placebo- and tolterodine-controlled phase 2 dose-finding study.	BJU International, (93) 71-77.
905-CL-015 Chapple CR et al, 2004	Randomized, double-blind placebo-and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder.	BJU International, (93) 303-310.
905-CL-018 Cardozo L et al, 2004	Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder.	J Urol, (172) 1919-1924.
Supportive evidence (uncontrolled clinical trials or other comparators than placebo)		
905-CL-019 Haab, F et al	Long-term open-label solifenacin treatment associated with persistence with therapy in patients with overactive bladder syndrome.	Eur Urol (47) 376-384.
905-EC-001 (STAR) Chapple CR et al, 2005	A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial.	Eur Urol, (48) 464-470.
Citations reporting pooled or subgroup analyses		
905-CL-015 **905-CL-018** Abrams P, Swift S, 2005	Solifenacin is effective for the treatment of OAB dry patients: A pooled analysis.	Eur Urology (48) 483-487.
905-CL-015 **905-CL-018** Brunton S, Kuritzky L. 2005	Recent developments in the management of overactive bladder: focus on the efficacy and tolerability of once daily solifenacin succinate 5mg. (Pooled analysis)	Curr Med Res Opin 21 (1) 71-80.
905-CL-015 **905-CL-018** Kelleher CJ et al, 2005	Improved quality of life in patients with overactive bladder symptoms treated with solifenacin. (Pooled analysis for QoL)	BJU International (95) 81-85.
905-CL-015 **905-CL-018** Payne CK, Kelleher C. 2007	Redefining response in overactive bladder syndrome. (Pooled analysis for QoL)	BJU Int (99) 101-106.
905-CL-013 **905-CL-014** **905-CL-015** **905-CL-018** Cardozo L et al, 2006	Reductions in overactive bladder-related incontinence from pooled analysis of phase III trials evaluating treatment with solifenacin. (Subgroup analysis)	Int Urogynecol J (17) 512-519.

Trial/First author	Protocol title/Publication title	Publication citation
905-CL-013 **905-CL-014** **905-CL-015** **905-CL-018** Garely AD. 2004	Solifenacin succinate once daily is superior to placebo in all major overactive bladder symptoms in four trials: results in women. (Subgroup analysis)	Obstetr Gynecol 103 (S4) 129S.
905-CL-013 **905-CL-014** **905-CL-015** **905-CL-018** Millard RJ, Halaska M. 2006	Efficacy of solifenacin in patients with severe symptoms of overactive bladder: A pooled analysis. (Subgroup analysis)	Curr Med Res Opin 22 (1) 41-48.
905-CL-013 **905-CL-014** **905-CL-015** **905-CL-018** Kelleher C, Cardozo L. 2006	Solifenacin: as effective in mixed urinary incontinence as in urge urinary incontinence. (Subgroup analysis)	Int Urogynecol J (17) 382-388.
905-CL-013 **905-CL-014** **905-CL-015** **905-CL-018** Chapple CR et al, 2006	Solifenacin significantly improves all symptoms of overactive bladder syndrome. (Pooled analysis)	Int J Clin Pract 60 (8) 959-966.
905-CL-013 **905-CL-014** Gittelman M et al, 2003	Two randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, multi-center studies assess the efficacy and safety of daily oral administration of 10mg YM905 versus placebo in male and female subjects with overactive bladder. (Pooled analysis)	J Urol 169 (S4) 349
905-CL-013 **905-CL-014** **905-CL-015** **905-CL-018** **905-CL-019** Staskin DR, Alexis ETE. 2006	Short- and long-term efficacy of solifenacin treatment in patients with symptoms of mixed urinary incontinence. (Sub-group analysis)	BJU Int (97) 1256-1261
905-CL-015 **905-CL-018** **905-CL-019** Wagg A et al, 2006	Efficacy and tolerability of solifenacin in elderly subjects with overactive bladder syndrome: A pooled analysis.	Am J Geriatr Pharmacol (4) 14-24.

8. Results of Trials

The submission claimed the data indicate for the primary outcome, the mean number of micturitions per 24 hours, that treatment with solifenacin (5 and 10 mg combined or 10 mg alone) results in a statistically significant decrease in the number of micturitions per 24 hours at 4 weeks: -0.96 (95% CI: -1.13, -0.79) and 12 weeks -1.17 (95% CI: -1.35, -1.00) compared with placebo.

For the secondary outcome, the proportion of patients achieving less than 8 micturitions per 24 hours, the data indicate that treatment with solifenacin (5 and 10 mg combined or 10 mg

alone) results in a statistically greater proportion of patients with a mean of less than 8 micturitions per 24 hours at 4 weeks: RD=0.11 (95% CI: 0.08, 0.14); 8 weeks: RD=0.15 (95% CI: 0.12, 0.18) and 12 weeks: RD=0.14 (95% CI 0.11, 0.17) compared with placebo.

For the secondary outcome, the proportion of patients becoming continent, the data indicate that treatment with solifenacin (5 and 10 mg combined or 10 mg alone) results in a statistically greater proportion of patients becoming continent at 4 weeks: RD=0.17 (95% CI: 0.13, 0.21); 8 weeks: RD=0.16 (95% CI: 0.12, 0.21) and 12 weeks: RD=0.17 (95% CI 0.13, 0.22) compared with placebo.

For the secondary outcome, the proportion of patients with no urgency episodes, the data indicate that treatment with solifenacin (5 and 10 mg combined) results in a statistically greater proportion of patients with no urgency episodes at 4 weeks: RD=0.07 (95% CI: 0.04, 0.11); 8 weeks: RD=0.08 (95% CI: 0.04, 0.12) and 12 weeks: RD=0.07 (95% CI 0.03, 0.12) compared with placebo.

For the secondary outcome, proportion of patients with no episodes of nocturia, the data indicate that treatment with solifenacin (5 and 10 mg combined and 10 mg alone) results in a statistically greater proportion of patients with no episodes of nocturia at 12 weeks: RD=0.04 (95% CI 0.04, 0.07) compared with placebo. No differences in the proportion of patients with no episodes of nocturia were observed at 4 and 8 weeks between the treatment groups.

SOLIFENACIN VERSUS TOLTERODINE

The results of the meta-analyses comparing the effectiveness of solifenacin and tolterodine are provided below.

Change in mean number (SD) of micturitions per 24 hours at 4 and 12 weeks: solifenacin versus tolterodine

	4 weeks				12 weeks			
	Solifenacin		Tolterodine		Solifenacin		Tolterodine	
Trial	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
905-CL-005	70	-2.33 (2.61)	37	-1.79 (2.04)				
905-CL-015	530	-1.77 (2.69)	249	-1.40 (2.59)	530	-2.40 (3.06)	250	-1.88 (3.00)
905-EC-001	556	-2.12 (2.43)	571	-1.53 (2.38)	556	-2.42 (2.63)	571	-2.18 (2.88)
Meta-analysis WMD (95% CI)	**-0.52 (-0.74, -0.30)[a]**				-0.05 (-0.94, 0.84)[b]			

Bold typography indicate statistically significant differences between groups
WMD=weighted mean difference
[a] fixed effects model
[b] random effects model as I^2>50%

Responder analysis

Trial	4 weeks			8 weeks			12 weeks		
	Sol n/N	Tol n/N	RD (95% CI)[a]	Sol n/N	Tol n/N	RD (95% CI)[a]	Sol n/N	Tol n/N	RD (95% CI)[a]
<8 micturitions per 24 hours									
905-CL-015	104/548	51/266	0.02	129/548	54/266	0.01	161/548	65/266	0.03
905-EC-001	142/556	130/571	(-0.02, 0.05)	187/556	193/572	(-0.03, 0.05)	208/556	202/571	(-0.01, 0.07)
Becoming continent									
905-CL-015	123/299	61/157	0.04	140/299	67/157	0.06	152/299	76/157	**0.07**
905-EC-001	144/364	133/378	(-0.02, 0.09)	190/364	170/377	(0.00, 0.12)	218/364	191/378	**(0.01, 0.13)**
No urgency episodes									
905-CL-015	103/525	41/250	0.04	134/525	51/250	0.04	164/525	62/250	0.05

905-EC-001	101/556	81/566	(0.00, 0.07)	150/556	171/566	(0.00, 0.08)	187/556	171/566	(0.00, 0.09)
No nocturia episodes									
905-CL-015	50/475	29/232	-0.01	60/475	31/232	-0.01	79/475	35/232	0.00
905-EC-001	66/479	69/496	(-0.04, 0.02)	85/479	96/496	(-0.05, 0.02)	100/479	111/496	(-0.04, 0.04)

Bold typography indicate statistically significant differences between groups
Sol=solifenacin, Tol=tolterodine, RD=risk difference

[a] results of a meta-analysis conducted during the evaluation using RevMan, all results from fixed effects model, unless otherwise indicated

For PBAC's view of the results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that solifenacin has significant advantages in effectiveness over placebo but is associated with more toxicity.

The PBAC agreed that although the evidence presented supports this claim, this does not reflect the patient population in whom listing is sought.

10. Economic Analysis

The submission presented a preliminary (trial-based) economic evaluation. The choice of a cost-effectiveness approach versus placebo was considered appropriate. The resources included were drug costs and GP consultations to manage dry mouth.

The trial-based incremental cost/extra patient with a mean of < 8 micturitions per 24 hours over 12 weeks was estimated to be <$15,000.

The trial-based incremental cost/ extra patient becoming continent over 12 weeks was estimated to be <$15,000.

The trial-based incremental cost/ extra patient without urgency episodes over 12 weeks was estimated to be <$15,000.

The trial-based incremental cost/ extra patient without nocturia episodes over 12 weeks was estimated to be <$15,000.

The submission presented four modelled economic evaluations, each based on a different definition of response. The choice of the cost-utility approach versus placebo was considered appropriate. The resources included were drug costs, GP consultations for dry mouth, and costs associated with invasive treatment of OAB.

The base case modelled incremental discounted cost/extra QALY gained over two years was estimated to fall:

- in the range $45,000 – 75,000, in the model where definition of response is less than 8 micturitions per 24 hours;
- in the range $15,000 – $45,000, in the model where definition of response is no episodes of urinary incontinence;
- in the range $75,000 – $105,000, in the model where definition of response is no episodes of urgency;
- in the range $75,000 – $105,000, in the model where definition of response is no episodes of nocturia.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The financial cost/year to the PBS (excluding co-payments) was estimated by the submission to be up to <$10 million in Year 3. This was considered a likely under-estimate.

12. Recommendation and Reasons

The PBAC agreed that the acceptability of a placebo comparator depended upon the restriction being able to confine the use of this product to the proposed population, i.e. where treatment with oxybutynin has failed or is not tolerated. This is unlikely to be the case because the definition of failure and intolerance in the requested restriction were not described and any definitions are unlikely to be effective because of the large placebo effect observed in the clinical trials. As a consequence the pool of patients who would be eligible for the requested restriction would be broader than the intended population. There would be a substantial risk that, in practice, as a restricted benefit listing, solifenacin would become second line, or most likely, first line treatment, because it is known that propantheline is rarely used, instead of oxybutynin. Strengthening the restriction to an Authority required listing, would be problematic as it would be difficult for the prescriber to provide evidence that the patient met the authority requirements and compliance activities by Medicare Australia would not be possible.

Even if the above issues relating to the ability to enforce the restriction were to be resolved, the inclusion criteria of the trials forming the primary source of evidence for the submission, did not require patients to have failed or not tolerated oxybutynin treatment. A subgroup of patients from the trials may have been representative of the population for whom listing is sought because a proportion of patients enrolled in four of the eight trials had undergone previous treatment with anti-cholinergics (including oxybutynin) for OAB. The submission did not present any analyses examining whether previous failure or intolerance to oxybutynin varies treatment effect from solifenacin. Thus, although the evidence presented supported the claim of superior clinical effectiveness over placebo, there were insufficient clinical data to inform the cost effectiveness of solifenacin in the patient population for which PBS listing is requested i.e. where treatment with oxybutynin has failed or is not tolerated.

The PBAC also questioned which outcome should be used as a basis for the economic evaluation. The submission presented results for an extensive range of secondary outcomes. The PBAC considered that with a condition such as overactive bladder one outcome is likely to be more clinically meaningful than another. The four economic models presented in the submission, each based on a different definition of response raised the question of which cost per QALY should apply. The PBAC considered the definition of cost/QALY for specific responses to be uninformative because applying the same utility values to different definitions of response was not appropriate. The results in the four models were thus driven by the differences in the results for each endpoint, rather than by the different utilities for each response, and, as noted above, there was uncertainty about the applicability of the patients to the requested restriction from whom these results were measured. It was also noted that the models were particularly sensitive to small differences in the utility weights with the two health states (responder and non-responder). There was thus considerable uncertainty in the results of the economic models.

Overall, the PBAC considered that the data presented in the submission did not match the patient population for whom PBS subsidy was sought, resulting in clinical and economic uncertainties. The submission was therefore rejected on the basis of uncertain clinical benefit 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

Arrow Pharmaceuticals is disappointed with this outcome, however acknowledges the PBAC comments and concerns. Arrow Pharmaceuticals wishes to address these issues and will continue to work with the PBAC towards finding a mutually acceptable outcome to provide an efficacious and tolerable solution for the many patients who suffer from Overactive Bladder.