PUBLIC SUMMARY DOCUMENT
Product: Oxybutynin, transdermal patches, 36 mg (releasing approximately 3.9 mg per 24 hours), Oxytrol®
Sponsor: Hospira Pty Ltd

Date of PBAC Consideration: November 2008

1. Purpose of Application
The submission sought a restricted benefit listing for the treatment of urge urinary incontinence or urgency due to detrusor instability as second line therapy in patients who cannot tolerate oral oxybutynin or propantheline.

2. Background
At its March 2008 meeting the PBAC rejected an application to list oxybutynin transdermal patches as a restricted benefit for the treatment of symptoms of urge urinary incontinence and urgency because of uncertainty regarding the population that would use the transdermal patch and the application of the results from the clinical trials, uncertainty regarding the comparative clinical effectiveness of the patch, and uncertain cost effectiveness. (See also Public Summary Document of March 2008).

Oral oxybutynin has been listed on the PBS as a Restricted benefit for detrusor overactivity since 1996.

3. Registration Status
Oxybutynin transdermal patch was TGA registered on 10 May 2007 for the treatment of overactive bladder with symptoms of urinary frequency, urgency or incontinence or any combination of these symptoms.

4. Listing Requested and PBAC's View
Restricted benefit
Urge urinary incontinence or urgency due to detrusor instability in a patient who cannot tolerate oral oxybutynin or propantheline.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Oxybutynin transdermal patch will provide an alternative dosing option of oxybutynin for the treatment of symptoms of urge urinary incontinence and urgency due to detrusor instability in patients unable to tolerate the oral dose form.

6. Comparator
The submission nominated placebo as the main comparator. Supportive comparisons with solifenacin and tolterodine were also included in the submission. Neither solifenacin or tolterodine are PBS listed.

For PBAC's view see Recommendation and Reasons.

7. Clinical Trials

No changes were made to the trial data presented in the previous submission. The re-submission presented two randomised trials comparing transdermal oxybutynin with placebo in patients with overactive bladder. The re-submission also presented one randomised trial comparing transdermal oxybutynin with oral oxybutynin in patients with overactive bladder in its evaluation of the safety of TD oxybutynin. However, data presented as supporting evidence in the previous submission was presented as the key evidence in the re-submission (Trials 009 and 011).

The trials published at the time of the submission were:

Trial ID	Publication title	Publication citation
Direct randomised trials – key evidence		
Trial 099009 (Phase III) Dmochowski RR, et al	For The Transdermal Oxybutynin Study Group. Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence.	Dmochowski RR, et al. *Journal of Urology,* 2002, 168 (2): 58-586.
Trial 000011 (Phase IIIB) Dmochowski RR, et al	For The Transdermal Oxybutynin Study Group. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence.	Dmochowski RR, et al. *Urology,* 2003, 62 (2): 237-242.
Direct randomised trials – supportive evidence for safety		
Trial 096017 (Phase II) Davila GW, et al	A short-term, multicentre, randomised double-blind dose titration study of the efficacy and anticholinergic side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence.	Davila GW, et al. *Journal of Urology,* 2001, 166 (1): 140-145.
Supplementary randomised trial		
Sand P, et al	Oxybutynin transdermal system improves the quality of life in adults with overactive bladder: a multicentre, community-based, randomised study (Multicentre assessment of Transdermal Therapy in OAB with oxybutynin - MATRIX).	Sand P, et al. *BJU International,* Apr 2007 99 (4): 836-44.
Meta-analyses of direct randomised trials		
Dmochowski RR, et al	Transdermal oxybutynin in the treatment of adults with overactive bladder: combined results of two randomised clinical trials	Dmochowski RR, et al. *World Journal of Urology,* Sep 2005 23 (4): 263-70.

8. Results of Trials

No new data were presented in the re-submission. The trials reported small clinical benefits over placebo (in the meta-analysis of the direct randomised trials, the median change from baseline in daily urinary incontinence episodes at the end of treatment was -3.0 for the participants who received transdermal oxybutynin versus -2.0 for those who received placebo) which were close to conventional thresholds of statistical significance. Transdermal oxybutynin and tolterodine results were similar, but these were not formally analysed to assess non-inferiority. All these trial results were limited to 12 weeks' duration.

No new toxicity data were presented in the re-submission. Transdermal oxybutynin was associated with more application site reactions than either placebo or tolterodine. There were more withdrawals over 12 weeks from transdermal oxybutynin (11 %) than from tolterodine (3 %) or from placebo (1 %).

9. Clinical Claim

The submission claimed that TD oxybutynin was more effective than placebo, but was associated with more adverse events (application site reactions). The re-submission also claimed that TD oxybutynin was non-inferior to tolterodine and solifenacin. The claim of non-inferiority of TD oxybutynin compared with tolterodine was not well justified due to the uncertainty regarding the clinical significance of the pre-specified equivalence interval and the formulation of tolterodine used in Trial 011 differing from those currently registered for use in Australia. The claim of non-inferiority of TD oxybutynin compared with solifenacin was also not well justified due to differences in disease severity of patients enrolled in the respective trials and that a significantly greater proportion of patients treated with TD oxybutynin discontinued treatment compared with those treated with solifenacin.

10. Economic Analysis

An updated modelled economic evaluation was presented. The model structure was substantially unchanged from the previous submission; however efficacy estimates were changed to reflect the change in comparator.

The results of the primary stepped economic evaluation using the pooled results from Trials 009 and 011 over 12 weeks estimated the incremental cost per extra quality adjusted life year (QALY) gained as < $15,000. Testing the upper and lower confidence intervals (CI) of the relative risk of achieving continence when being treated with TD oxybutynin compared to placebo resulted in a 95% CI for the incremental cost per QALY ranging from TD oxybutynin being dominant (i.e. decreased cost, increased effectiveness - upper 95% CI) to placebo being dominant (i.e. increased cost, decreased effectiveness - lower 95% CI).

11. Estimated PBS Usage and Financial Implications

The submission used patient full year equivalents (PFYEs) to estimate PBS usage at between 10,000 and 50,000 PFYEs in Year 5 of listing at an estimated financial cost per year to the PBS (excluding co-payments) minus any savings in use of other drugs of < $10 million in Year 5.

12. Recommendation and Reasons

The PBAC accepted that the resubmission requested listing for a more limited patient population than previously, namely to those patients unable to tolerate oral oxybutynin.

The PBAC confirmed its March 2008 advice that the main comparator in this population was placebo for no PBS-subsidised medicine and that the secondary clinical comparison with tolterodine was informative even though tolterodine was not listed on the PBS.

The PBAC recalled its March 2008 concerns that the key trials submitted did not recruit patients who represented those who would be eligible according to the requested restriction. Specifically, neither trial recruited patients intolerant to oral oxybutynin. Trial 009 recruited a majority of previously untreated patients and Trial 011 recruited patients who had experienced a beneficial response to anticholinergic therapy and then were sufficiently tolerant to this therapy to be stabilised for at least six weeks. This was important because the essential clinical claim of the submission was that switching from oral oxybutynin to transdermal oxybutynin retained superior effectiveness over placebo and similar effectiveness to tolterodine whilst reducing the toxicity that led to intolerance. Trial participants also had

moderate to severe disease of many years' duration, whereas the requested restriction would encompass less severe disease of shorter duration.

The PBAC therefore concluded that the results of these trials would overestimate the extent of effectiveness in the population targeted by the requested restriction. The trials reported small clinical benefits over placebo (in the meta-analysis of the direct randomised trials, the median change from baseline in daily urinary incontinence episodes at the end of treatment was -3.0 for the participants who received transdermal oxybutynin versus -2.0 for those who received placebo) which were close to conventional thresholds of statistical significance. Transdermal oxybutynin and tolterodine results were similar, but these were not formally analysed to assess non-inferiority. All these trial results were limited to 12 weeks' duration. Longer-term results relied on an assumption that in a symptomatic disease, patients would only persist with therapy if they perceived a sufficient response. There was no basis provided to verify this assumption.

Transdermal oxybutynin was associated with more application site reactions than either placebo or tolterodine. There were more withdrawals over 12 weeks from transdermal oxybutynin (11 %) than from tolterodine (3 %) or from placebo (1 %).

The PBAC considered that the modelled economic evaluation was uncertain. In particular, the translation of achieving complete continence (a secondary outcome of the trials) into utilities was uncertain, both in terms of the transformation to utilities and the impact of assumed discontinuation rates which acted as a surrogate for a loss of effectiveness over time. The expected further waning of effectiveness beyond the 12-month time horizon of the modelled economic evaluation was important given that participants in the key trials were around 60 years of age. The re-analysis of the model with new assumptions about the utility distributions presented in the Pre-PBAC response was not accepted because it was not presented in sufficient detail to allow a clear determination of the appropriateness of this late re-analysis compared with the approach in the resubmission. In addition, while the PBAC noted the argument in the submission that the SF-6D was subject to floor effects, the PBAC did not accept that this was a sufficient basis to reject its general preference of relying on the results of accepted multi-attribute utility instruments reported in the key trials and considered that it would be appropriate to present SF-6D based utility scores in addition to the weights presented in the submission.

The PBAC noted a substantial potential for use of transdermal oxybutynin beyond the requested restriction. The PBAC decided not to recommend listing on the basis of uncertain comparative clinical effectiveness in the population who would be eligible according to the requested restriction and the resulting 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

The sponsor will be considering its position regarding any future course of action.