**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:** March 2008

## 1. Purpose of Application
The submission sought a Restricted benefit listing for the treatment of symptoms of urge urinary incontinence and urgency.

## 2. Background
This was the first time oxybutynin transdermal patches had been considered by the PBAC.

## 3. Registration Status
Oxytrol was TGA registered on the 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
Treatment of symptoms of urge urinary incontinence and urgency.

The PBAC did not comment on the requested restriction.

## 5. Clinical Place for the Proposed Therapy
Oxytrol is used for the treatment of overactive bladder with symptoms of urinary frequency, urgency or incontinence or any combination of these symptoms.

## 6. Comparator
Oral oxybutynin was identified as the appropriate main comparator. Placebo was identified as the secondary comparator.

*See Recommendation and Reasons for PBAC's view.*

## 7. Clinical Trials
The submission presented one randomised trial comparing transdermal oxybutynin with oral oxybutynin in patients with overactive bladder. The submission also presented two randomised trials comparing transdermal oxybutynin with placebo in patients with overactive bladder.

The trials as published at the time of the submission are presented in the table below.

| Trial ID | Publication title | Publication citation |
|---|---|---|
| **Direct randomised trials** | | |
| Trial 096017 (Phase II)<br><br>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. | *Journal of Urology,* 2001, 166 (1): 140-145. |
| Trial 099009 (Phase III) | For The Transdermal Oxybutynin Study Group. Efficacy and safety of transdermal oxybutynin in | *Journal of Urology,* 2002, 168 (2): 58-586. |

| | | |
|---|---|---|
| Dmochowski RR, et al | patients with urge and mixed urinary incontinence. | |
| Trial 000011 (Phase IIIB)<br><br>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. | *Urology,* 2003, 62 (2): 237-242. |
| **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). | *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 | *World Journal of Urology,* Sep 2005 23 (4): 263-70. |

## 8. Results of Trials

The results of the trials are summarised in the table below:

**Proportion of participants achieving complete continence (zero incontinent episodes per day) at endpoint on all doses of transdermal and oral oxybutynin**

| Trial ID | TD oxybutynin | Comparator | *Tolterodine* | Risk Difference (95% CI) | Relative Risk (95% CI) |
|---|---|---|---|---|---|
| | n/N (%) | n/N (%) | n/N (%) | | |
| **TD oxybutynin versus oral oxybutynin** | | | | | |
| **017** | 8/37 (21.6) | 10/35 (28.6) | NA | -6.95% (-27.1%,13.3%) | 0.76 (0.34, 1.70) |
| **TD oxybutynin versus placebo** | | | | | |
| **009** | 18/120 (15.0) | 11/127 (8.7) | NA | 6.3% (-1.7%, 14.9%) | 1.73 (0.85, 3.51) |
| **011** | 47/121 (38.8) | 26/117 (22.2) | 47/123 (38.2) | **16.6% (4.9%, 27.9%)** | **1.75 (1.16, 2.62)** |
| **Pooled 009 & 011**: random effects model<br>Test for heterogeneity=0.00 (p=0.98), $I^2$*=0%* - RR<br>Test for heterogeneity=2.31 (p=0.13), $I^2$*=56.7%* - RD | | | | **11.0% (0.0%, 21.0%)** | **1.74 (1.23, 2.48)** |

Notes: CI=Confidence Interval, Statistically significant results are bolded.

The results from trial 017 comparing transdermal oxybutynin to oral oxybutynin show no statistically significant difference in the proportion of patients achieving full continence.

Trial 017 was a dose titration study and patients were initiated at one of three levels according to the patient's prior stable daily oral oxybutynin dose. After two and four weeks, the dose was increased if patients regarded their side effects as being absent or mild.

The results show that five of the eight patients achieving full continence received a transdermal oxybutynin dose that is not TGA-approved (1 on 26 $cm^2$ and 4 on 52 $cm^2$).

The following table summaries the anti-cholinergic adverse events from the Phase II/III trials:

| Adverse Event | TD oxybutynin (double-blind) N (%) | TD placebo N (%) | Oral oxybutynin N (%) | TD oxybutynin (double-blind and open label) N (%) |
|---|---|---|---|---|
| | (n=547) | (n=249) | (n=38) | (n=663) |
| Dry mouth | 41 (7.5) | 13 (5.2) | 22 (57.9) | 57 (8.6) |
| -related | 41 (7.5) | 13 (5.2) | 22 (57.9) | 57 (8.6) |
| Constipation | 19 (3.5) | 7 (2.8) | 10 (26.3) | 30 (4.5) |
| -related | 17 (3.1) | 5 (2.0) | 10 (26.3) | 26 (3.9) |
| Dizziness | 15 (2.7) | 6 (2.4) | 6 (15.8) | 23 (3.5) |
| -related | 10 (1.8) | 3 (1.2) | 5 (13.2) | 15 (2.3) |
| Nausea | 18 (3.3) | 8 (3.2) | 7 (18.4) | 25 (3.8) |
| -related | 10 (1.8) | 3 (1.2) | 6 (15.8) | 14 (2.1) |
| Somnolence | 6 (1.1) | 1 (0.4) | 6 (15.8) | 8 (1.2) |
| -related | 6 (1.1) | 1 (0.4) | 6 (15.8) | 8 (1.2) |
| Palpitations | 4 (0.7) | 0 | 3 (7.9) | 5 (0.8) |
| -related | 2 (0.4) | 0 | 3 (7.9) | 2 (0.3) |
| Vision abnormal | 12 (2.2) | 3 (1.2) | 4 (10.5) | 16 (2.4) |
| -related | 11 (2.0) | 2 (0.8) | 4 (10.5) | 15 (2.3) |
| Dysuria | 10 (1.8) | 1 (0.4) | 3 (7.9) | 14 (2.1) |
| -related | 6 (1.1) | 1 (0.4) | 3 (7.9) | 6 (0.9) |
| Urinary retention | 2 (0.4) | 0 | 1 (2.6) | 2 (0.3) |
| -related | 2 (0.4) | 0 | 1 (2.6) | 2 (0.3) |

Overall, the safety profile for transdermal oxybutynin appeared favourable compared to placebo. The anticholinergic event profile for transdermal compared to oral oxybutynin also appeared favourable. A greater proportion of patients treated with transdermal oxybutynin (3.9mg/day) experienced an application site adverse event.

## 9. Clinical Claim

The submission claimed that TD oxybutynin is equivalent to oral oxybutynin in terms of comparative effectiveness, but has a superior adverse event profile.

The PBAC did not agree with the therapeutic claim in the submission that the transdermal patch oxybutynin was equivalent to oral oxybutynin in terms of efficacy but with fewer side effects. The PBAC noted non-inferiority was not shown in Trial 017, with a lower CI for the difference of -17% when the trial specified non-inferiority at -15%. Additionally, five of the eight patients achieving full continence on the transdermal patch received an oxybutynin dose that is not TGA-approved (1 on 26cm$^2$ and 4 on 52cm$^2$). The response to the transdermal patches may therefore be over-inflated.

## 10. Economic Analysis

A modelled economic evaluation was presented. The model was a decision tree analysis, with a single cycle of a one year period. There were four health states used in the model to which utility values were applied. The key drivers of the model appeared to be the estimate of effectiveness of TD oxybutynin, the utility values applied to the health states and a number of cost estimates.

From the primary economic evaluation, the estimated incremental cost per Quality-Adjusted Life-Year (QALY) gained compared to oral oxybutynin was in the range of $15,000 to $45,000.

A secondary economic evaluation of transdermal oxybutynin compared to placebo produced an incremental cost per QALY gained in the range of $15,000 to $45,000.

## 11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated to be between $10 and $30 million in Year 3.

The PBAC considered that these estimates were likely to be underestimated.

## 12. Recommendation and Reasons

The PBAC noted the differences in pharmacology between the oral and transdermal patches of oxybutynin. Oral oxybutynin undergoes an extensive first-pass metabolism by the cytochrome P450 system producing an active metabolite, N-desethyloxybutynin (N-DEO). N-DEO appears to contribute greatly to the anticholinergic side-effects associated with the oral administration of oxybutynin (i.e. dry mouth), and it is thought that the transdermal administration of oxybutynin, which avoids the first-pass (gastrointestinal and pre-systemic) metabolism, could result in fewer anticholinergic side effects with similar efficacy by lowering plasma concentrations of N-DEO. On the other hand, the metabolite N-DEO may contribute to the activity of the drug on the human detrusor muscle as *in vitro* studies it has been shown to have similar activity to oxybutynin.

The PBAC acknowledged that, at the hearing, the sponsor was open to the Committee considering either first-line or second-line listing for the transdermal patch. A second-line listing, however, did not match the trial populations in the clinical evidence presented, which were responder populations who were able to sufficiently tolerate any anticholinergic or other adverse events to enable treatment for at least a six-week period. The submission did not present sufficient evidence in patients who failed or were intolerant to oral anticholinergic treatments.

The PBAC also considered that it is unlikely that a patient failing first-line treatment will not seek further treatment. Therefore, placebo was not considered a sufficient second line comparator; this part of the requested listing should have also resulted in a comparison with solifenacin and tolterodine, noting that neither product is PBS-listed.

The PBAC did not agree with the therapeutic claim in the submission that the transdermal patch oxybutynin was equivalent to oral oxybutynin in terms of efficacy but with fewer side effects. Non-inferiority was not shown in Trial 017, with a lower CI for the difference of -17% when the trial specified non-inferiority at -15%. Additionally, five of the eight patients achieving full continence on the transdermal patch received an oxybutynin dose that is not TGA-approved (1 on 26cm$^2$ and 4 on 52cm$^2$). The response to the transdermal patches may therefore be over-inflated.

The PBAC also considered that the lower adverse events (particularly dry mouth) may be associated with lower effectiveness given the potential for the N-DEO metabolite to be active on the detrusor muscle. The transdermal patch is also associated with application site reactions and the PBAC noted that the discontinuation rates between transdermal patch oxybutynin and oral oxybutynin did not differ.

The Committee noted the price requested for the transdermal patch was considerably greater that of the oral dose. The economic model used to justify this price was considered overly complex. The PBAC was of the view that the most important aspect of the model should be the impact of adverse events on costs and utilities. This aspect was not clear from the model provided.

The PBAC therefore rejected the submission based on uncertainty regarding the population that would use the transdermal patch and the application of the results from the clinical trials, which were made up of responders to oral anticholinergics; uncertainty regarding the comparative clinical effectiveness of the patch; and uncertain cost effectiveness. The price advantage over the oral formulation was considered unjustified.

## 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.