

PUBLIC SUMMARY DOCUMENT

Product: SOLIFENACIN, tablet, 5 mg and 10 mg (as succinate), Vesicare®

Sponsor: Sigma Pharmaceuticals Pty Ltd

Date of PBAC Consideration: July 2010

1. Purpose of Application

To request a Restricted Benefit listing for detrusor overactivity in a patient who cannot tolerate oral oxybutynin.

2. Background

At the July 2007 meeting, the PBAC rejected a submission to list solifenacin as a restricted benefit for 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 on the basis of uncertain clinical benefit and uncertain cost-effectiveness.

Full details in the July 2007 Public Summary Document

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

Detrusor overactivity in a patient who cannot tolerate oral oxybutynin.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Detrusor overactivity (idiopathic or neurogenic) is the most common cause of overactive bladder syndrome. It is characterised by involuntary detrusor contractions during the filling phase of the micturition cycle which may be spontaneous or provoked. In a patient with normal sensation, urgency is likely to be experienced just before the leakage episode. There is a significant impact on the quality of life for patients with urge or stress incontinence.

Solifenacin would provide an additional treatment option for detrusor overactivity for patients who cannot tolerate oral oxybutynin.

6. Comparator

The submission nominated transdermal oxybutynin as the comparator. The PBAC considered this appropriate.

7. Clinical Trials

The re-submission presented three new solifenacin flexible dose (5-10 mg daily) trials (VENUS, VIBRANT, SUNRISE trials); as well as three TD oxybutynin (oxybutynin transdermal patch) versus placebo trials to conduct an indirect comparison of solifenacin versus oxybutynin TD.

The solifenacin fixed dose (5 mg or 10 mg daily) versus placebo trials (CL-013, CL-014, CL-015, CL-018 and CL-037), with a 12-week double-blind comparative duration, had been previously considered by the PBAC.

The key trials and associated reports published at the time of submission are as follows:

Trial ID/First author	Protocol title/ Publication title	Publication citation
Common reference placebo		
Solifenacin		
Chu F et al 2009	Efficacy and safety of solifenacin succinate 10mg once daily, a multicentre, phase III, randomised, double-blind, placebo-controlled, parallel-group trial in patients with overactive bladder.	Current Therapeutic Research 2009; 70 (6):405-420.
Chapple C 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 2004; 93(3): 303-310.
Cardozo L et al 2004	Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder.	Journal of Urology 2004; 172(5 I): 1919-1924.
Yamaguchi O et al 2007	Randomized, double-blind, placebo- and propioverine-controlled trial of the once daily antimuscarinic agent solifenacin in Japanese patients with overactive bladder.	BJU International 2007; 100(3): 579-587.
Appell R et al 2007	The effects of solifenacin in continent and incontinent patients with overactive bladder.	European Urology Supplements 2007; 6(2): 274-274.
Karram M et al 2009	Treatment with solifenacin increases warning time and improves symptoms of overactive bladder: results from VENUS, a randomized, double-blind, placebo-controlled trial.	Urology 2009; 73(1): 14-18.
Toglia M.	Solifenacin improves urgency symptoms as assessed by voiding diaries and patient-reported outcomes in patients with overactive bladder.	Abtr 155
Toglia M.	Solifenacin improves warning time significantly compared to placebo in patients with overactive bladder.	Abtr 123
Toglia M et al 2009	Solifenacin for overactive bladder: patient-reported outcomes from a large placebo-controlled trial.	Postgraduate Medicine 2009; 121(5): 151-158.
Vardy MD et al. 2009.	Effects of solifenacin on overactive bladder symptoms, symptom bother and other patient-reported outcomes: results from VIBRANT – a double-blind, placebo-controlled trial.	Int J Clin Pract 2009; 63(12): 1702-1714.

Trial ID/First author	Protocol title/ Publication title	Publication citation
Cardozo L et al 2008	Solifenacin in the treatment of urgency and other symptoms of overactive bladder: Results from a randomized, double-blind, placebo-controlled, rising-dose trial.	BJU International 2008; 102(9): 1120-1127.
Oxybutynin Patches (transdermal)		
Dmochowski R et al (2002)	Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence.	Journal of Urology 2002; 168(2): 580-586.
Dmochowski R et al (2003)	Comparative efficacy and safety of transdermal oxybutynin ad oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence.	Urology 2003; 62(2): 237-242.
Homma Y and Koyama N (2006)	Minimal clinically important change in urinary incontinence detected by a quality of life assessment tool in overactive bladder syndrome with urge incontinence.	Neurology & Urodynamics 2006; 25(3): 228-235.
Meta-analyses of direct randomised trials		
Abrams, Swift (2005)	Solifenacin is effective for the treatment of OAB dry patients: A pooled analysis.	European Urology 2005; 48(3): 483-487.
Cardozo et al (2006)	Reductions in overactive bladder-related incontinence from pooled analysis of phase III trials evaluating treatment with solifenacin.	International Urogynecology Journal and Pelvic Floor Dysfunction 2006; 17(5): 512-519.
Millard, Halaska (2006)	Efficacy of solifenacin in patients with severe symptoms of overactive bladder: A pooled analysis.	Current Medical Research and Opinion 2006; 22(1): 41-48.
Payne, Kelleher (2007)	Redefining response in overactive bladder syndrome.	BJU International 2007; 99(1): 101-106.

8. Results of Trials

The outcomes common to all studies presented in the re-submission are: mean change from baseline in the number of incontinence episodes per 24 hours; percentage of patients achieving continence at trial endpoint; mean change from baseline in the number of micturitions (episodes of urination) per 24 hours; mean change from baseline in the volume of urine voided per micturition; and change in quality of life (King's Health Questionnaire).

The mean change from baseline in the number of incontinence episodes per 24 hours was the primary outcome in the TD oxybutynin trials. The primary outcome in the solifenacin fixed dose trials (Trials CL-013, CL-014, CL-015, CL-018 and CL-037) was the mean change from baseline in the number of micturitions per 24 hours. The primary outcomes for the solifenacin flexible dose trials (VENUS, VIBRANT and SUNRISE) were all based on changes in urgency. As none of these same urgency outcomes were reported in the oxybutynin TD trials, they cannot be used in the indirect comparison of solifenacin versus oxybutynin TD.

INCONTINENCE EPISODES

The TD oxybutynin trials reported change in incontinence episodes as the primary study endpoint. This was a secondary outcome in the fixed dose and flexible solifenacin trials. The

results for the outcome ‘mean change from baseline in the number of incontinence episodes per 24 hours’ are summarised below:

The mean changes in the common reference arm of the two sets of trials vary, with the placebo response rates in the TD oxybutynin trials being higher. This may indicate some important differences between the trials, for example in the baseline disease severity of the two sets of trials.

In three of the comparisons the active treatment did not show a statistically significant change from baseline in mean number of incontinence episodes per 24 hours compared to placebo (solifenacin 5 mg and 10 mg fixed dose arms of CL018 and TD oxybutynin in Dmochowski (2002)).

The meta-analyses demonstrated that treatment with fixed dose 5 mg and 10 mg solifenacin, flexible dose solifenacin and TD oxybutynin resulted in a statistically significant reduction in the mean number of incontinence episodes per 24 hours compared with placebo. The results of the indirect comparisons demonstrated there is no difference between solifenacin (5 or 10 mg fixed dose or flexible dose) and TD oxybutynin.

The lowest 95% CI interval for the indirect estimate of the effect of solifenacin versus TD oxybutynin was +0.39 (for the solifenacin flexible dose comparison). The re-submission stated that the one median change from the meta-analysis of Dmochowski et al (2002) and Dmochowski et al (2003) equates to a mean value of 0.52. The re-submission stated that the lower (positive) 95% CIs obtained in the meta-analysis (UL: 0.39) for the indirect comparison supported non-inferiority of the two treatments.

PROPORTION WITH COMPLETE CONTINENCE

The results for the secondary outcome of proportion of patients with complete continence at study endpoint are summarised below. This outcome was not measured in the VIBRANT trial.

The placebo response rates in the solifenacin and TD oxybutynin trials vary markedly, with a much lower placebo response rate observed in the TD oxybutynin trials. Patients with more severe incontinence have been demonstrated to show a lesser improvement in this outcome, as it is a ‘higher hurdle’ to achieve when the patient is starting off with a greater number of incontinence episodes per 24 hours. Patients in the TD oxybutynin trials appeared to have more severe disease, which may explain the discrepancy, alternatively it may indicate that the patients in the trials may differ significantly and thus performing an indirect comparison based on these trials may not be valid.

The meta-analyses demonstrated that treatment with fixed dose 5 mg and 10 mg solifenacin, flexible dose solifenacin and TD oxybutynin (RR, but not RD) resulted in a statistically significantly greater proportion of patients with complete continence at study end compared with placebo. The results of the indirect comparisons demonstrated there is no difference between solifenacin (5 or 10 mg fixed dose or flexible dose) and TD oxybutynin. No MCID has been nominated for this outcome.

MICTURITIONS

The fixed-dose solifenacin trials had change in micturition frequency as the primary study endpoint. For all other trials this was a secondary endpoint. The results for the outcome mean change from baseline in the number of micturitions per 24 hours are summarised below.

The placebo response rates across the solifenacin and TD oxybutynin trials appear to be comparable. The meta-analyses demonstrated that treatment with fixed dose 5 mg and 10 mg solifenacin, flexible dose solifenacin and TD oxybutynin resulted in a statistically significant reduction in mean number of micturitions per 24 hours compared with placebo. The results of the indirect comparisons demonstrated there was no difference between solifenacin (5 mg fixed dose or flexible dose) and TD oxybutynin. A statistically significant difference in the mean number of micturitions was observed in the indirect comparison between solifenacin fixed dose 10 mg and TD oxybutynin, in favour of solifenacin.

The lowest 95% CI value for any of the comparisons where no difference was found was 0.35 micturitions per 24 hours, from the solifenacin flexible dose versus TD oxybutynin comparison. This value was much lower than the values of 1 to 1.9 micturitions per day used in sample size calculations for the solifenacin fixed dose studies, suggesting non-inferiority based on this criteria.

The re-submission presented new toxicity data, including data for the solifenacin flexible dose trials and the TD oxybutynin trials.

There was no significant difference in withdrawals due to adverse events with solifenacin compared with placebo.

There were no differences between solifenacin and oxybutynin TD in the risk of developing most anticholinergic-associated adverse events (dizziness, dysuria, somnolence, constipation, palpitations, abnormal/blurred vision). Dry mouth occurred more frequently with all doses/treatment regimes of solifenacin than oxybutynin TD. Nausea occurred more frequently with solifenacin than oxybutynin TD, using the fixed-dose solifenacin (and not flexible dose solifenacin) studies.

The re-submission provided additional data on potential safety concerns beyond those identified in the clinical trials by providing the most recent Periodic Safety Update Report (PSUR). During the reporting period there was a fatal case of angioedema. Based on this case, the US Product Information was updated regarding the risk of angioedema with airway obstruction.

9. Clinical Claim

The re-submission described solifenacin as non-inferior to TD oxybutynin, based on equivalent efficacy and safety levels via indirect comparison.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis.

The equi-effective doses were estimated in the submission as solifenacin 6.50 mg and TD oxybutynin 3.90 mg are equi-effective. The PBAC did not accept the equi-effective doses proposed in the submission.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed/year (accounting for market share as necessary) was estimated by the submission to be in the range 100,000 – 200,000 in Year 3 and Year 5. This was compared with 50,000 – 100,000 in Year 3 in the previous submission.

The financial cost per year to the PBS minus any savings in use of other drugs was estimated by the submission to be less than \$10 million in Year 3 and Year 5. This was higher compared with the previous submission.

12. Recommendation and Reasons

The PBAC recommended the listing of solifenacin on the PBS as a Restricted Benefit item for detrusor overactivity in patients who cannot tolerate oral oxybutynin on a cost minimisation basis with transdermal oxybutynin. The PBAC noted that the average daily dose of solifenacin in the flexible dose solifenacin trials of VENUS and VIBRANT were 7.47 mg and 7.80 mg respectively and hence considered that the equi-effective doses of 7.47 mg of solifenacin and 3.9 mg transdermal oxybutynin were reasonable.

The PBAC did not accept the equi-effective doses proposed in the submission of 6.5 mg solifenacin and 3.9 mg transdermal oxybutynin, based on IMS/AMI data (an Australian healthcare setting dose equivalence ratio calculation), considering the average daily dose of solifenacin from the flexible dose trials presented in the submission appropriate for the purpose of estimating equi-effective doses.

Based on the totality of the evidence presented, the PBAC considered solifenacin tablets to be of non-inferior efficacy and safety to transdermal oxybutynin.

The PBAC considered further economic uncertainty lay in the utilisation estimates, with the submission underestimating the utilisation of solifenacin. The PBAC noted that the utilisation estimates were based primarily on the use of solifenacin in the private market of which only a proportion of the patients would meet the requested PBS restriction and therefore may be overestimated, and some switching from PBS subsidised transdermal oxybutynin. For latter, the PBAC noted that the PBS prescriptions for transdermal oxybutynin were underestimated, as they were based on five months of data and not adjusted for 12 months. Further the PBAC considered that there could be other sources of patients who may utilise solifenacin, such as those switching from privately prescribed tolterodine and patients who are currently untreated. The PBAC considered that all such sources were not sufficiently accounted for in the estimation of market growth.

The PBAC considered that there was a high likelihood for the use of solifenacin outside the requested restriction to first line therapy.

The PBAC considered that a grandfather clause was not appropriate.

The PBAC welcomed and noted the consumer comments provided in relation to the solifenacin submission, which were all from prescribers.

Recommendation:

SOLIFENACIN, tablet, 5 mg and 10 mg (as succinate), Vesicare®

Restriction: Restricted Benefit
Detrusor overactivity in a patient who cannot tolerate oral oxybutynin.

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

Sigma welcomes this recommendation by the PBAC to list Vesicare, thus giving patients suffering from symptoms of overactive bladder but cannot tolerate oral oxybutynin, another oral treatment option.