PUBLIC SUMMARY DOCUMENT
Product: Agomelatine, tablet, 25 mg, Valdoxan®
Sponsor: Servier Laboratories (Australia) Pty Ltd
Date of PBAC Consideration: November 2010

1. Purpose of Application
The submission sought a Restricted Benefit listing for major depressive disorders.

2. Background
This drug had not previously been considered by the PBAC.

3. Registration Status
Agomelatine was TGA registered on 9 August 2010 for the treatment of major depression in adults including prevention of relapse.

4. Listing Requested and PBAC's View
Restricted benefit
Major depressive disorders

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy
Major depression is a condition characterised by a persistent feeling of depressed mood and loss of interest or pleasure in addition to a number of other psychological and somatic symptoms.

The submission proposed that the place in therapy of agomelatine is to provide another first-line treatment option for major depression that has a different side-effect profile to existing treatments, due to agomelatine's differing mechanism of action.

6. Comparator
The submission nominated venlafaxine as the comparator.

The PBAC did not agree that this was the appropriate comparator. *See Recommendations and Reasons.*

7. Clinical Trials
The submission presented two randomised, double-blinded trials, CL3-035 and CL3-036, comparing agomelatine with venlafaxine in patients with major depressive disorders. CL3-035 was a titrated dose study comparing agomelatine 25-50 mg daily to venlafaxine 75-150 mg daily. CL3-036 compared fixed daily doses of agomelatine 50 mg to venlafaxine 150 mg.

Details of the published studies presented in the submission are in the table below.

Trial ID / First Author	Protocol title / Publication title	Publication citation
Trial CL3-035 Lemoine P, et al.	Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: Randomized, double-blind comparison with venlafaxine.	*Journal of Clinical Psychiatry* 2007; 68 (11): 1723-1732
Trial CL3-036 Kennedy SH, et al.	A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR.	*Journal of Clinical Psychopharmacology* 2008; 28 (3): 329-333

8. Results of Trials

The primary outcome of Trial CL3-035 was the "getting off to sleep" category of the Leeds Sleep Evaluation Questionnaire; agomelatine showed statistically significant larger improvements on this measure than venlafaxine. The primary outcome of Trial CL3-036 was changes in the Sex Effects Scale (SEX-FX); there were no statistically significant differences between agomelatine and venlafaxine in the change in SEX-FX score although agomelatine showed advantage in orgasm sub-scores.

Trial CL3-035 showed no statistically significant differences between agomelatine and venlafaxine in changes in the secondary outcome of HAM-D17 scores from baseline to 6 weeks (ANCOVA estimate 0.92, 95% CI -0.49, 2.32, the estimate of 0.92 favoured agomelatine). There were also no differences in Hamilton Anxiety Scale (HAM-A) scores, HAM-A psychic anxiety scores or somatic anxiety scores between agomelatine and venlafaxine. The ANCOVA estimate of differences in Clinical Global Impression (CGI) scores between agomelatine and venlafaxine was statistically significant at both 6 weeks and 24 weeks, with agomelatine treated patients more improved. There were no statistically significant differences in HAM-D17 responders and remitters at 6 weeks in Trial CL3-035. There were statistically significantly more CGI responders among agomelatine treated patients at 6 weeks but the difference was not significant at 24 weeks.

Trial CL3-036 showed no statistically significant differences between agomelatine and venlafaxine in the secondary outcome of change from baseline in MADRS scores at 6 weeks (ANCOVA estimate -0.30, 95% CI -2.16, 1.55). Mean MADRS scores were the same in agomelatine and venlafaxine treated patients at 24 weeks. There were no statistically significant differences between agomelatine and venlafaxine in MADRS responder and remitter rates at 12 weeks and 24 weeks.

There were statistically significantly lower rates of non-serious adverse events leading to discontinuation in agomelatine treated patients reported in the mandatory phases of Trials CL3-035 and CL3-036. In addition, there were statistically significantly fewer 'all adverse events' in the 12-week mandatory phase of Trial CL3-036. There were statistically significantly lower rates of nausea and dizziness in agomelatine treated patients in Trial CL3-035.

In pooled analyses of results from Trials CL3-035 and CL3-036 there were statistically significant fewer discontinuations overall and discontinuations due to adverse events in agomelatine treated patients.

9. Clinical Claim

The submission claimed that agomelatine was non-inferior to venlafaxine in terms of comparative effectiveness in the treatment of major depressive disorder and superior to venlafaxine with fewer treatment discontinuations.

The lack of inclusion of a placebo arm in the two comparative trials of agomelatine and venlafaxine (CL3-035, CL3-036) meant that PBAC was unable to exclude the possibility of assay failure for these studies and was thus unable to accept the submission's claim for the non-inferiority of agomelatine with venlafaxine or SSRIs in terms of antidepressant efficacy. *See Recommendation and Reasons*.

10. Economic Analysis

A modelled, cost-utility analysis was presented. The model used four health states: depressed, remitted, well (occurring after remitted for six months), and dead. The cycle length was one-month and the model horizon was 3 years.

The base case incremental cost-effectiveness ratio (ICER) was calculated to be in the range of $15,000 to $30,000 per extra quality adjusted life year (QALY) gained.

The Product Information for agomelatine recommends that "Liver function tests should be performed in all patients: at initiation of treatment and then periodically after around six weeks (end of acute phase), after around twelve and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated."

The PBAC noted the economic model provided with the initial submission inappropriately excluded the costs of liver function tests, and that when these were included, the base case ICER increased by less than $5,000/QALY. The PBAC considered that any future submission would need to incorporate the costs of liver function tests into the economic analysis.

11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated in the submission to be in the range of $10 - $30 million in Year 5. There is potential for the net cost per year for the PBS to be greater than the estimate in the submission due to possibly higher average daily doses for agomelatine in practice compared to Trial CL3-035 and higher uptake rates than assumed in the submission.

12. Recommendation and Reasons

The PBAC considered that the submission's nomination of venlafaxine as the main comparator for agomelatine was inappropriate, as although based on Medicare data for the period April 2009 to March 2010, venlafaxine has the largest single agent share of the antidepressant market, the selective serotonin uptake inhibitors (SSRIs - sertraline, citalopram, escitalopram, fluoxetine, paroxetine and fluvoxamine) account for 54% of the total antidepressant market. Even when the proportion of use of SSRIs for indications other than major depression is taken into account, the SSRIs as a group remain an appropriate comparator for agomelatine.

Additionally, PBAC has previously recognised that venlafaxine is cost-effective compared to the SSRIs [PBPA Therapeutic Relativity Sheets] and although duloxetine

and desvenlafaxine, the two most recently PBS listed antidepressants, used venlafaxine as the main comparator in their submissions, venlafaxine, duloxetine and desvenlafaxine all belong to the selective serotonin noradrenaline reuptake inhibitor (SNRI) class of antidepressants, whereas agomelatine is the first in a new class of antidepressants. The PBAC thus considered the submission should have presented a comparison of the efficacy and safety of agomelatine against the SSRIs as well as venlafaxine, and that substantiation of a claim of superiority to venlafaxine also required demonstration of superiority over the SSRIs.

The SSRI comparison is particularly important in view of the two agomelatine studies reported in the evaluation in which the anti-depressant efficacy of both agomelatine and paroxetine or fluoxetine was not significantly different from placebo. This so called "assay failure" phenomenon is well recognised in trials in depression. Because of this possibility, the European Medicines Agency (EMEA) argues that a conclusion of non-inferiority cannot be made without the inclusion of a placebo arm to demonstrate efficacy of both active treatment comparisons. The lack of inclusion of a placebo arm in the two comparative trials of agomelatine and venlafaxine (CL3-035, CL3-036) meant that PBAC was unable to exclude the possibility of assay failure for these studies and was thus unable accept the submission's claim for the non-inferiority of agomelatine with venlafaxine or SSRIs in terms of antidepressant efficacy. The acceptance of this claim by PBAC was further hampered because trials -035 and -036 did not have anti-depressant efficacy as a primary outcome, and neither was designed as a non-inferiority trial. Additionally, the average daily dose of venlafaxine in trial -035 (83.8 mg) was less than the average dose used in Australian practice (119.8 mg), which may have biased the trial results against venlafaxine.

The PBAC then noted that the submission's claim that, at the proposed price advantage over venlafaxine, agomelatine is a cost-effective treatment, also rests upon acceptance that fewer discontinuations will occur with agomelatine treatment. These fewer discontinuations are then assumed to translate to better persistence rates in the Australian population treated with agomelatine, which in turn is assumed to translate into better response and remission rates and better patient outcomes. The Committee had a number of problems with this approach, as follows:

- Discontinuation rates cannot be assumed to be persistence rates. Discontinuation is indirectly related to adherence or persistence: multiple factors affect adherence and persistence with antidepressant drugs and no single factor, such as adverse events, has a direct relationship such as that proposed in the submission. Although, as stated at the sponsor hearing, increased persistence to anti-depressants results in reduced rates of relapse, the submission had not shown that the reduced discontinuation rate observed for agomelatine compared with venlafaxine in the clinical trials would result in increased persistence in clinical practice;
- Most interventions that successfully address anti-depressant adherence target factors other than adverse events;
- The Intent to Treat analyses for -035 and -036 already take into account the differential discontinuation rates between agomelatine and venlafaxine but the results in terms of HAM-D, MADRS, remission and recurrence rates are similar for both agents, making it inappropriate to model improvements in remission or recurrence associated with agomelatine over those associated with venlafaxine; and

- The use of the multiplier of 1.7 to adjust the discontinuation rates in the trial to those measured in Australian PBS data is inappropriate, as PBS data are not an appropriate source of data on adherence and persistence; and
- The assumption that patients discontinuing initial treatment do not go on to another antidepressant is unlikely to reflect clinical practice in which a proportion of discontinuing patients will go on to another antidepressant.

Additional to these concerns, the PBAC noted the economic model provided with the initial submission inappropriately excluded the costs of liver function tests, and that when these were included the base case incremental cost-effectiveness ratio (ICER) increased by less than $5,000/QALY but remained in the range of $15,000 to $30,000 per QALY. The PBAC considered that any future submission would need to incorporate the costs of liver function tests into the economic analysis.

The PBAC thus rejected the application to list agomelatine on the PBS because of uncertainty around the claim that agomelatine is superior to venlafaxine and the resultant uncertainty in the economic analysis. The Committee considered that even if a future submission was able to demonstrate that agomelatine is superior (or non-inferior) to venlafaxine, it will also be necessary to demonstrate its clinical superiority to SSRIs to adequately justify a cost-effective (or cost-minimisation) listing against venlafaxine.

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

Servier is working to achieve PBS-listing for agomelatine in a timely manner so that Australians can have equitable access to this new antidepressant.

With respect to the lack of a placebo arm in the key clinical trials, Servier notes that a trial in which the test drug is statistically significantly superior to the active control is, according to the EMEA (2002), a possible alternative route to demonstrating efficacy in depression.