PUBLIC SUMMARY DOCUMENT
Product: AGOMELATINE, tablet, 25 mg, Valdoxan®
Sponsor: Servier Laboratories (Australia) Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application

The re-submission sought a Restricted Benefit listing for major depressive disorders.

2. Background

At the November 2010 meeting, the PBAC rejected an application for PBS-listing of agomelatine because of uncertainty around the claim that agomelatine was superior to venlafaxine and the resultant uncertainty in the economic analysis. The Committee considered that the submission's nomination of venlafaxine as the main comparator was inappropriate, as although based on Medicare data for the period April 2009 to March 2010, venlafaxine had the largest single agent share of the anti-depressant market, the SSRIs (sertraline, citalopram, escitalopram, fluoxetine and fluvoxamine) accounted for 54% of the total anti-depressant market. Even when the proportion of use of SSRIs for indications other than major depression was taken into account, the SSRIs as a group remained an appropriate comparator for agomelatine.

A copy of the Public Summary Document (PSD) from the November 2010 meeting is available at http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-agomelatine-nov10

3. Registration Status

Agomelatine was TGA registered on 9 August 2010 for 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 was as an alternative first-line treatment option for major depression, with a different mechanism of action and adverse event profile, to current pharmacological treatments.

6. Comparator

As in the previous submission, the re-submission nominated venlafaxine as the main comparator. In response to the PBAC's request for a comparison of agomelatine with the SSRIs, the re-submission also presented a comparison of agomelatine with SSRIs: fluoxetine, sertraline and escitalopram.

The PBAC considered that the SSRIs were the more appropriate main comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The re-submission presented no new trial data comparing agomelatine with venlafaxine (CL3-035 and CL3-036). Publication details of these trials have been previously reported in the November 2011 PSD.

The re-submission presented and meta-analysed the results of an additional four randomised trials comparing agomelatine with SSRIs (CL3-045, CL3-046, CL3-056 and CL3-063), and discussed the systematic review and meta-analysis by Schueler *et al* (2011) of duloxetine and venlafaxine compared to other antidepressants including SSRIs in major depression. Details of the studies published at the time of the submission are presented in the table below.

Trials and associated reports presented in the submission

Trial ID/first author	Protocol title/ Publication title	Publication citation
Direct randomised trials (agomelatine vs SSRIs)		
CL3-045 Hale A *et al*.	Superior antidepressant efficacy results of agomelatine versus fluoxetine in severe MDD patients: A randomized, double-blind study	*International Clinical Psychopharmacology* 2010; 25: 305-314
CL3-046 Kasper S *et al.*	Efficacy of the novel antidepressant agomelatine on the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder: a randomized, double-blind comparison with sertraline	*The Journal of Clinical Psychiatry* 2010; 71(2): 109-120
Meta-analyses comparing venlafaxine/duloxetine vs SSRIs		
Schueler YB *et al*	A systematic review of duloxetine and venlafaxine in major depression, including unpublished data.	*Acta Psychiatrica Scandinavica* 2011; 123: 247–65

8. Results of Trials

Comparative effectiveness

Agomelatine versus venlafaxine:

The resubmission presented no new trial data comparing agomelatine with venlafaxine (CL3-035 and CL3-036). The main outcome of HAM-D17 & Montgomery-Asberg depression rating scale (MADRS) scores were the secondary outcomes of the agomelatine vs venlafaxine trials. The primary outcomes were the Leeds Sleep Evaluation Questionnaire (CL3-035) and the Sex Effects Scale score (CL3-036).

The results of CL3-035 and CL3-036 have been previously reported in the November 2010 PSD.

Agomelatine versus SSRIs:

The primary outcome for Trial CL3-045 and a secondary outcome for Trials CL3-046, CL3-056 and CL3-063 was the difference in the adjusted mean change from baseline HAM-D17 scores. The pooled estimate for this outcome was presented as a sensitivity analysis in the re-

submission's meta-analyses with difference in the last post-baseline HAM-D 17 score presented as primary outcome in the meta-analysis.

The adjusted mean change in HAM-D17 total scores from baseline comparing agomelatine with SSRIs for those trials published is shown in the following table.

Results of HAM-D17 total scores comparing agomelatine with SSRIs – adjusted mean change from baseline

Trial ID	Agomelatine			SSRI			Treatment effect[a] SSRI-Ago (95%CI)
	n	Mean baseline (SD)	Mean change (SD)	n	Mean baseline (SD)	Mean change (SD)	
Mandatory period							
CL3-045 fluoxetine (8 wks)	247	28.5 (2.7)	-17.3 (7.3)	257	28.7 (2.5)	-16.0 (8.4)	**1.49 (0.20, 2.77)**
CL3-046 sertraline (6 wks)	150	26.1 (2.8)	-15.8 (7.3)	156	26.5 (3.0)	-14.4 (8.7)	**1.68 (0.15, 3.20)**
Optional extension period (Weeks 0 to 24)							
CL3-045 fluoxetine	247	*28.5 (2.7)*	-19.9 (8.3)	257	*28.7 (2.5)*	-18.9 (9.6)	-
CL3-046 sertraline	150	26.1 (2.8)	-17.7 (8.4)	156	26.5 (3.0)	-16.4 (10.3)	NR

Abbreviations: Ago, agomelatine; CI, confidence interval; HAM-D, Hamilton Depression Rating scale; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; wks, weeks
[a] adjusted for centre (random effect) and baseline as a covariate
Bolded results are statistically significant

During the mandatory period of the four trials, agomelatine was associated with larger reductions in HAM-D17 scores, although the differences between agomelatine and the SSRI comparator were only statistically significantly different in Trials CL3-045 and CL3-046. The pooled result was statistically significantly different in favour of agomelatine However, considering that the nominated MCID was 1.5 points, the PBAC considered it unlikely that this difference was clinically important. For the optional extension analysis (to Week 24), there were no statistically significant differences between agomelatine and the SSRI comparator in the two trials (CL3-045 and CL3-063) reporting adjusted mean change from baseline. However, only patients who were 'responders' in the mandatory period were able to enter the optional extension period, so it could be expected that the two treatments would not differ.

The pooled analyses showed that there were statistically significantly higher HAM-D17 responder rates (reduction of at least 50% from baseline) for agomelatine compared to SSRI in both the mandatory and optional extension analyses. However, there were no statistically significant differences in the proportion of HAM-D17 remitters in either period.

The between-arm differences in the mean last post-baseline Clinician Global Impression (CGI) severity of illness (CGI-S) and CGI global improvements (CGI-I) scores were generally small and favoured agomelatine. The pooled results showed that there was a statistically significant difference favouring agomelatine for both CGI-S and CGI-I in the mandatory period, and for CGI-I in the optional extension analyses.

The odds of being a CGI responder were higher for agomelatine-treated patients in the mandatory period, but there were no significant differences in the optional extension period. There were no differences in CGI remitter rates for either the mandatory or the extension period.

The re-submission presented new toxicity data comparing agomelatine with SSRIs and discussed the latest Periodic Safety Update Report.

Agomelatine versus venlafaxine:
There were statistically significant fewer discontinuations overall and discontinuations due to adverse events in agomelatine treated patients.

Agomelatine versus SSRIs:
In the pooled analyses, there were statistically significantly fewer agomelatine-treated patients discontinuing overall and due to adverse events compared to SSRI-treated patients during the mandatory period. However, there were no statistically significant differences in discontinuation rates during the optional extension period, with the point estimates favouring SSRIs.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The re-submission stated that the conclusion and the claim had not changed from the November 2010 submission i.e. agomelatine was non-inferior in terms of efficacy and superior in terms of discontinuation from treatment to the primary comparator venlafaxine.

The PBAC reaffirmed that substantiation of a claim of non-inferiority to venlafaxine would first require demonstration of superiority over the SSRIs.

The re-submission also described agomelatine as superior in terms of comparative efficacy and superior in terms of comparative safety over SSRIs. This was not accepted by the PBAC.

The PBAC considered that the evidence provided in the submission was not sufficient to support the claim that agomelatine was superior in terms of comparative efficacy and safety to the SSRIs. *See Recommendation and Reasons.*

10. Economic Analysis

The re-submission presented a cost minimisation analysis against venlafaxine. The re-submission presented an updated model which was still based on the clinical claim that fewer discontinuations would occur with agomelatine compared to venlafaxine. These fewer discontinuations were assumed to translate to better adherence, a claim that has not previously been accepted by PBAC.

From the updated model, the incremental cost per quality adjusted life-year (QALY) gained was less than $15,000 for the base-case, which included liver function tests (LFTs) costs.

11. Estimated PBS Usage and Financial Implications

The re-submission's estimate of the likely number of patients treated per year was between 50,000 and 100,000 in Year 5, at a net cost per year to the PBS of less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC reaffirmed that, as agomelatine is the first in a new class of antidepressants, substantiation of a claim of non-inferiority to venlafaxine firstly requires demonstration of superiority over the SSRIs. The PBAC considered that the SSRIs were the more appropriate main comparator for agomelatine as agomelatine will be used in the first line treatment of depression. The PBAC further considered that the evidence provided in the submission was not sufficient to support the claim that agomelatine was superior in terms of comparative efficacy and safety to the SSRIs.

The PBAC expressed a number of concerns with the trial data comparing agomelatine with the SSRIs as a secondary clinical comparator. There were concerns surrounding the selective exclusion of 5 earlier trials (CL3-014, CL3-022, CL3-023, CL3-024 and CL3-030). The impact of excluding potentially relevant trials was uncertain. The sponsor in its Pre Sub-Committee Response explained that these trials lacked the methodological improvements seen in subsequent studies and used a fixed dose regimen rather than the titrating dose regimen applied in clinical practice. However, the key trial CL3-036 in the submission comparing agomelatine 50 mg with venlafaxine 150 mg was also a fixed dose trial and was not excluded on this basis. Of the four included trials, the PBAC noted that both SSRI comparators in two trials (CL3-045 and CL3-046) may have been inadequately dosed. In addition, the fluoxetine dose in trial CL3-045 could be titrated from 20 mg up to 40 mg from week 4, whereas the agomelatine dose could be titrated up from 25 mg to 50 mg at week 2, which could favour agomelatine.

The PBAC noted that the nominated main depression outcomes (HAM-D17 and CGI) used in the resubmission were not the primary outcomes for trials CL3-046 (rest/activity cycle), CL3-056 (polysomnographic sleep efficiency index) and CL3-063 (global satisfaction on sleep score), although the HAM-D17 total score was the primary outcome for CL3-045.

During the mandatory period of the four trials, agomelatine was associated with larger reductions in HAM-D17 scores, although the differences between agomelatine and the SSRI comparator were only statistically significantly different in Trials CL3-045 and CL3-046. The pooled result (SSRI-agomelatine) was statistically significantly different in favour of agomelatine However, the PBAC considered that the differences were unlikely to be clinically important, given the pre-defined MCID for change from baseline in HAM-D17 score was 1.5. For the optional extension analysis (to Week 24), the PBAC noted that there were no statistically significant differences between agomelatine and the SSRI comparator in the two trials (CL3-045 and CL3-063) reporting adjusted mean change from baseline. There were statistically significantly more HAM-D17 responders (reduction of at least 50% from baseline) among agomelatine-treated patients, but no statistically significant differences in HAM-D17 remitter rates

The PBAC noted that there were inconsistencies in the CGI results. The difference in mean CGI-I (global improvement) was statistically significantly in favour of agomelatine for the mandatory and optional extension periods, but was only statistically significant in the mandatory period for CGI-S (severity of illness). The PBAC considered that the small

differences reported were unlikely to be clinically important. The odds of being a CGI responder were higher for agomelatine-treated patients in the mandatory period, but there were no significant differences in the optional extension period. There were no differences in CGI remitter rates for either the mandatory or the extension period.

There was some evidence supporting the lower discontinuation rates associated with agomelatine in the mandatory period, but not the optional extension period of the SSRI trials. The PBAC concerns regarding a claim of superiority based on discontinuation rates remain:

- Discontinuation rates cannot be assumed to be persistence rates. Multiple factors can affect adherence and persistence.
- Intention-to-treat analyses already account for the differential discontinuation rates in the efficacy outcomes; and
- A proportion of discontinuing patients will go on to another antidepressant in clinical practice.

The resubmission presented no new trial data comparing agomelatine with venlafaxine (CL3-035 and CL3-036). The main outcome of HAM-D17 & Montgomery-Asberg depression rating scale (MADRS) scores were the secondary outcomes of the agomelatine vs venlafaxine trials. The primary outcomes were the Leeds Sleep Evaluation Questionnaire (CL3-035) and the Sex Effects Scale score (CL3-036).

For Trial CL3-035, there was no statistically significant difference between agomelatine and venlafaxine at the end of the mandatory period (6 weeks) in the mean last post-baseline HAM-D17 scores. Again, the PBAC considered interpretation of these results was limited by the potential under-dosing of venlafaxine in this trial. For Trial CL3-036, there were no statistically significant differences in the mean last post-baseline MADRS scores at Week 6 between agomelatine- and venlafaxine-treated patients. There were no statistically significant differences in HAM-D17/MADRS responder and remitter rates between agomelatine and venlafaxine for the individual trials and the pooled analyses during the mandatory period. The PBAC considered that interpretation of the pooled data was limited by the use of different depression measurement scales, the differences in dosing schedules and the differences in trial durations.

The submission presented a cost minimisation analysis against venlafaxine. As in the previous submission, the PBAC noted uncertainties regarding both the equi-effective doses of agomelatine and venlafaxine and the updated model which was still based on the clinical claim that fewer discontinuations would occur with agomelatine compared to venlafaxine. These fewer discontinuations were assumed to translate to better adherence, a claim that has not previously been accepted by PBAC.

As noted above, the PBAC considered that the SSRIs were the more appropriate main comparator for agomelatine, the first in a new class of antidepressants, as agomelatine will be used in the first line treatment of depression and is more likely to substitute for SSRIs than the more expensive SNRIs in clinical practice. The estimates in Section E of the submission supported this assumption.

The PBAC rejected the submission on the basis that superior clinical effectiveness and safety over SSRIs had not been demonstrated.

The PBAC also acknowledged and noted the consumer comments received in its consideration of agomelatine.

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 has met with the PBAC Chairman and is working towards achieving a PBS-listing in a timely manner for agomelatine.