

## **PUBLIC SUMMARY DOCUMENT**

**Product:** AGOMELATINE, tablet, 25mg, Valdoxan<sup>®</sup>

**Sponsor:** Servier Laboratories (Australia) Pty Ltd

**Date of PBAC Consideration:** March 2012

### **1. Purpose of Application**

The resubmission sought a Restricted Benefit listing for major depressive disorders.

### **2. Background**

The PBAC has considered two previous submissions for agomelatine.

At the November 2010 meeting, the PBAC rejected an application for PBS-listing of agomelatine because of uncertainty in the economic analysis and the submission's choice of an inappropriate comparator.

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>

At the July 2011 meeting, the PBAC rejected a resubmission for PBS listing of agomelatine because superior clinical effectiveness and safety over SSRIs had not been demonstrated.

A copy of the PSD from the July 2011 meeting is available at <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-agomelatine-july11>

### **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 proposed 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 resubmission again proposed that the place in therapy of agomelatine is as an alternative first-line treatment option for major depressive disorders.

### **6. Comparator**

As in the previous submission, the resubmission nominated venlafaxine as the primary comparator. As previously, the resubmission also presented a comparison to SSRIs (fluoxetine, sertraline and escitalopram)

The PBAC reaffirmed that substantiation of a claim of non-inferiority to venlafaxine firstly requires demonstration of superiority over the SSRIs.

*For PBAC's view, see Recommendations and Reasons*

## 7. Clinical Trials

The re-submission presented no new trial data comparing agomelatine with venlafaxine (CL3-035 and CL3-036) or comparing agomelatine with SSRIs (CL3-045, CL3-046, CL3-056 and CL3-063). Publication details of these trials have been previously reported in the November 2010 and July 2011 PSDs.

The resubmission presented sensitivity analyses including additional data from three of the five excluded trials in the July 2011 submission (CL2-014, CL3-022, and CL3-030). Only CL2-014 had been published at the time of submission. Details are below:

<b>Trial ID / First author</b>	<b>Protocol title / Publication title</b>	<b>Publication citation</b>
CL2-014 Loo H, et al.	Determination of the dose of agomelatine, a melatonergic agonist and selective 5-HT <sub>2C</sub> antagonist, in the treatment of major depressive disorder: A placebo-controlled dose range study.	International Clinical Psychopharmacology 2002; 17: 239-247.

## 8. Results of Trials

### 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 same data presented in the July 2011 submission formed the base-case of agomelatine versus SSRIs comparisons in the current resubmission. The results have been previously reported in the July 2011 PSD. The PBAC previously considered that the evidence provided in the July 2011 submission was not sufficient to support the claim that agomelatine was superior in terms of comparative efficacy and safety to the SSRIs.

The resubmission argued that the reduction in HAM-D17 score is clinically relevant, as the difference between arms is 59% of the SSRI versus placebo difference of 2.0 points from the meta-analysis by Kirch *et al* (2002). The PBAC noted the Pre-Sub-Committee Response (p1) argument that an expert statement confirms that a HAM-D improvement of 59% is clinically relevant. However, the PBAC noted that the upper bound of the 95% CI for the difference in HAM-D17 scores is -0.45 points in favour of agomelatine, which is 22.5% of the SSRI versus placebo difference of 2.0 points. Therefore, the 95% CI contains values that are unlikely to be clinically important.

The PBAC noted that only one fixed dose trial (CL3-022; agomelatine 25 mg vs. fluoxetine 20 mg) was included in the sensitivity analysis of the mean change from baseline in HAM-D17 scores for the mandatory period and that there were no statistically significant differences between the agomelatine and SSRIs arms.

The PBAC noted that considering a non-inferiority margin of 1.0, 1.15 or 1.5, the pooled results for the sensitivity meta-analysis support a claim that agomelatine is non-inferior to SSRIs (upper bound of the 95% CI is 0.12 in favour of SSRIs).

The resubmission claimed that Trial CL3-045 is the “most robust” single study comparison of agomelatine with an SSRI. This trial was designed as a non-inferiority trial with HAM-D17 scores as the primary outcome. There was a statistically significantly larger mean reduction in HAM-D17 score in the agomelatine arm versus the fluoxetine arm (mean difference -1.49; 95% CI -2.77, -0.20). Similarly, the resubmission claimed that the difference is clinically relevant. However, the PBAC noted that the TGA clinical evaluator stated that the clinical relevance of the finding was marginal. In addition, the 95% CI included values which were unlikely to be clinically relevant (absolute difference of 0.20 points).

The PBAC noted the results of an additional “sensitivity analysis” conducted during the evaluation which included all trials with an agomelatine and a comparator SSRI arm reporting responder rates (except CL3-030 and NCT 00463242) which showed no statistically significant differences in responder rates between agomelatine and SSRIs.

The PBAC noted that there were no statistically significant differences in the proportion of HAM-D17 / MADRS remitters between the agomelatine and SSRI arms for the base-case and sensitivity analyses during the mandatory period and the optional extension period.

*For PBAC’s view of these results, see Recommendation and Reasons.*

The resubmission presented new toxicity data from the additional agomelatine and SSRIs trials included in the sensitivity analysis and the latest Periodic Safety Update Report (PSUR).

Agomelatine versus venlafaxine: There were statistically significantly fewer overall discontinuations and discontinuations due to adverse events (AEs) amongst agomelatine-treated patients compared to venlafaxine-treated patients. The PBAC’s concerns surrounding discontinuations still remain, i.e. discontinuations rates cannot be assumed to be adherence rates, the intention-to-treat analysis already account for differing discontinuation rates in efficacy outcomes, and a proportion of patients discontinuing will go on to another antidepressant.

Agomelatine versus SSRIs: There were statistically significantly lower overall discontinuation rates during the mandatory period associated with agomelatine versus SSRIs for the base-case analysis, but there were no statistically significant differences for the sensitivity analysis. There were statistically significant fewer agomelatine-treated patients discontinuing due to AEs during the mandatory period versus SSRI-treated patients for both the base-case and the sensitivity analysis. The PBAC’s concerns surrounding a claim of superiority based on discontinuation rates remain.

*For PBAC's view, see Recommendations and Reasons*

## **9. Clinical Claim**

The resubmission described agomelatine as non-inferior in terms of comparative antidepressant efficacy, superior in terms of improving sleep and superior in terms of comparative safety (as assessed by withdrawals due to AEs and less sexual dysfunction) compared to venlafaxine.

The PBAC did not accept the resubmission's new claim of superior safety of agomelatine over venlafaxine.

*For PBAC's view, see Recommendations and Reasons*

The resubmission described agomelatine as superior in terms of comparative efficacy and superior in terms of comparative tolerability compared to SSRIs. The PBAC considered that the evidence provided in the resubmission was not sufficient to support this claim.

## **10. Economic Analysis**

The resubmission presented a cost-minimisation analysis. Agomelatine 28.5 mg and venlafaxine 83.8 mg were estimated to be equi-effective, based on the flexible dosing trial, CL3-035.

*For PBAC's view, see Recommendations and Reasons*

## **11. Estimated PBS Usage and Financial Implications**

The resubmission estimated the likely number of patients per year to be between 50,000 and 100,000 in year 5 at an estimated cost to the PBS of less than \$10 million in year 5.

The PBAC considered the utilisation estimates in the resubmission to be highly uncertain.

*For PBAC's view, see Recommendations and Reasons*

## **12. Recommendation and Reasons**

The PBAC reaffirmed that substantiation of a claim of non-inferiority to venlafaxine firstly requires demonstration of superiority over the selective serotonin re-uptake inhibitors (SSRIs). The PBAC considered that the SSRIs are the more appropriate main comparators 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 is superior in terms of comparative efficacy and safety to the SSRIs.

The PBAC noted that the four trials informing the base case of this resubmission were the same as those presented in the July 2011 submission (CL3-045, CL3-046, CL3-056 and CL3-063), and that new sensitivity meta-analyses including additional data from three of the five trials excluded from the July 2011 submission (CL2-014, CL3-022, and CL3-030) were presented to compare agomelatine to SSRIs. The resubmission excluded trials CL3-023 and CL3-024 on the basis of 'assay sensitivity', and also excluded NCT 00463242, a flexible dosing trial with agomelatine and paroxetine arms. The PBAC considered exclusion of CL3-023 and CL3-024 on the basis of 'assay sensitivity' was not appropriate and considered that

the impact of excluding these three potentially relevant trials on the meta-analyses results was uncertain.

The PBAC noted that there were no statistically significant differences in the proportion of Hamilton Depression Rating scale 17 items (HAM-D 17)/ Montgomery and Asberg Depression Rating Scale (MADRS) remitters between the agomelatine and SSRI arms for the base case and sensitivity analyses during the mandatory period and the optional extension period. The PBAC also noted that only one fixed dose trial (CL3-022; agomelatine 25 mg versus fluoxetine 20 mg) was included in the sensitivity analysis of the mean change from baseline in HAM-D17 scores for the mandatory period and that there were no statistically significant differences between the agomelatine and SSRI arms. The PBAC also noted that the sensitivity analyses suggested statistically significantly higher responder (greater than or equal to 50 % reduction in HAM-D17 score from baseline) rates for patients treated with agomelatine versus patients treated with SSRIs during the mandatory period. However, the PBAC considered that the differences were unlikely to be clinically important. The results of the sensitivity analyses showed a smaller difference between agomelatine and the SSRIs than the base case pooled results (unchanged from July 2011), which the PBAC had considered provided an insufficient basis to support the claim of superior efficacy and safety of agomelatine in comparison to SSRIs. The PBAC hence concluded that the new meta-analyses presented in this resubmission provided insufficient evidence to alter this conclusion.

The PBAC noted that this resubmission presented the same trial data for the comparison of agomelatine to venlafaxine as the July 2011 and November 2010 submissions of trials CL3-035 and CL3-036. The PBAC further noted that trials CL3-035 and CL3-036 reported measures of depressive symptoms as secondary outcomes and that the primary outcomes were the Leeds Sleep Evaluation Questionnaire (CL3-035) and the Sex Effects Scale score (CL3-036). The PBAC hence considered no data were presented to alter its previous conclusion that the non-inferiority of agomelatine in comparison to venlafaxine in terms of anti-depressant efficacy was uncertain.

The PBAC noted that this resubmission claimed superior efficacy of agomelatine to venlafaxine in terms of improved sleep, which had not been claimed in the previous submission. The PBAC noted that patients treated with agomelatine perceived statistically significantly greater improvement in “getting to sleep” score of the Leeds Sleep Evaluation Questionnaire (LSEQ) compared to patients treated with venlafaxine from Week 1 to 6 in trial CL3-035. The PBAC however noted that this was one score on a four-point sleep scale and that trials CL3-056 and CL3-063 did not report statistically significant differences between agomelatine and escitalopram for the primary sleep outcomes.

The PBAC did not accept the submission’s new claim of superior safety of agomelatine over venlafaxine, claiming less sexual dysfunction, noting that there was not a statistically significant difference between agomelatine and venlafaxine in trial CL3-036 for the primary outcome of total Sex Effects Scale (SEX FX) score in remitted patients, nor in the sub-group of patients sexually active at baseline.

The PBAC considered the equi-effective doses estimated in the resubmission of agomelatine 28.5 mg and venlafaxine 83.8 mg to be uncertain, noting that the dose of venlafaxine in trial CL3-035 (150 mg), on which the equi-effective doses were based, was less than the

maximum recommended dose in the TGA-approved product information (225 mg). Further, as the cost minimisation analysis is based on the acceptance of non-inferior efficacy and safety of agomelatine to venlafaxine, the PBAC considered that the cost minimisation analysis was not supported by the clinical evidence presented in the resubmission.

The PBAC considered the exclusion of the costs of liver function tests from the economic model inappropriate and considered that liver function tests should have been included in the economic analysis.

The PBAC considered the utilisation estimates in the resubmission to be highly uncertain due to the potential for usage outside the requested restriction including use in the management of sleep disorders, uncertainty in the relative substitutions of SSRIs and SNRIs, uncertainty in the estimated market uptake rates and the assumed differences in the duration of therapy.

The PBAC therefore rejected the submission on the basis that superior clinical effectiveness and safety over SSRIs had not been demonstrated. The PBAC further considered that non-inferior efficacy and superior safety to venlafaxine 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**

The sponsor disagrees with the decision and refers you to [www.servier.com.au](http://www.servier.com.au) for further information.