PUBLIC SUMMARY DOCUMENT
Product: ASENAPINE, sublingual wafer, 5 mg and 10 mg (as maleate), Saphris®
Sponsor: Lundbeck Australia Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application

The submission sought an Authority required (STREAMLINED) listing for treatment, for up to 6 months, of an episode of acute mania or mixed episodes associated with bipolar I disorder, and maintenance treatment, as monotherapy, of bipolar I disorder. The submission also proposed the alternative listing of "treatment of bipolar I disorder".

2. Background

This drug had not been previously considered by the PBAC.

In a separate submission to the July 2011 meeting, the sponsor requested an Authority required (STREAMLINED) listing for asenapine for the treatment of schizophrenia.

3. Registration Status

Asenapine was TGA registered on 11 March 2011 for the following indications:

- Treatment of schizophrenia in adults;
- Treatment of acute manic or mixed episodes associated with bipolar I disorder in adults as monotherapy or in combination with lithium or sodium valproate;
- Prevention of relapse of manic or mixed episodes in bipolar I disorder in adults as monotherapy or in combination with lithium or sodium valproate.

4. Listing Requested and PBAC's View

Authority required (STREAMLINED)
Treatment, for up to 6 months, of an episode of acute mania or mixed episodes associated with bipolar I disorder.
Maintenance treatment, as monotherapy, of bipolar I disorder.

Alternatively, the submission states that "as monotherapy" could be removed from the restriction for maintenance treatment, depending on the decision of the TGA delegate, and the restriction be simplified to:

Authority required (STREAMLINED)
Bipolar I disorder.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Bipolar disorder occurs in at least 1% to 2% of the population. Characterised by distinct episodes of mania and depression, the impact of the illness is severe, impinging on relationships, career, self-esteem and longevity. Some episodes manifest with both manic and depressed symptoms—these 'mixed episodes' are usually a variant of mania. Most patients with bipolar disorder also experience periods of low-grade depression between the major mood episodes. Where symptoms are less severe and of shorter duration, the term hypomania is used. If patients have had at least one manic episode at any stage of their life, the condition

is termed bipolar I disorder. If there have been only hypomanic and depressed episodes, this is called bipolar II disorder.

The submission proposed that the place in therapy of asenapine is as an alternative treatment option to those agents currently listed on the PBS for the treatment of bipolar I disorder.

6. Comparator

The submission nominated olanzapine as the main comparator. The submission also presented a secondary comparison with quetiapine.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The basis of the submission is described below:

Monotherapy direct comparison: two direct randomised comparative trials (A7501004 and A7501005) and two associated continuation trials (A7501006 and A7501007) comparing asenapine with olanzapine. The comparisons between the asenapine and olanzapine were not an a priori objective in Trials A7501004 and A7501005, and were conducted post hoc.

Monotherapy (indirect comparison, placebo as common comparator): trials A7501004 and A7501005 comparing asenapine with placebo as well as four direct randomised comparative trials (Bowden 2005, McIntyre 2005, Vieta 2010 and D144CC00004) comparing quetiapine with placebo.

The submission did not present separate data for acute versus maintenance therapy. Analyses of the longer term efficacy of asenapine compared to olanzapine and quetiapine (monotherapy) are derived from the continuation trials (A7501006 and A7501007).

Adjunctive therapy to mood stabilisers (indirect comparison, placebo as common comparator): one direct randomised comparative trial (A7501008) and associated continuation trial (A7501009) comparing asenapine + mood stabiliser with placebo + mood stabiliser and two randomised trials (Sachs 2004 and Yatham 2007) comparing quetiapine with placebo, and two randomised comparative trials (Houston 2009 and Tohen 2002) comparing olanzapine with placebo as adjunctive therapy to a mood stabiliser. No longer term comparative analyses (beyond 6 weeks) of asenapine versus olanzapine and quetiapine were presented.

Studies Suppes 2009, Vieta 2008, D1447C00144 and Tohen 2004 were relapse prevention trials and were included only in the assessment of comparative safety.

Details of the trials published at the time of the submission are in the table below.

Trial ID	Protocol title/ Publication title	Publication citation
Asenapine vs olanzapine vs placebo (monotherapy)		
A7501004 McIntyre RS et al.	Asenapine in the treatment of acute mania in bipolar I disorder: A randomized, double-blind, placebo-controlled trial.	*Journal of Affective Disorders* 2010a; 122(1–2):27–38.

A7501005 McIntyre RS, et al.	A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states.	*Bipolar Disorders* 2009a: 11: 673–686.
A7501006 (Extension A7501004/5) McIntyre RS, et al.	Asenapine versus olanzapine in acute mania: a double-blind extension study.	*Bipolar Disorders* 2009b: 11: 815–826.
A7501007 (Extension A7501006) McIntyre RS, et al.	Asenapine for long term treatment of bipolar disorder: A double-blind 40-week extension study.	*Journal of Affective Disorders* 2010b; 126(3):358-65.
Quetiapine vs placebo (monotherapy)		
Bowden 2005 Bowden CL, et al. Ketter TA, et al.	A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. Rates of remission/euthymia with quetiapine monotherapy compared with placebo in patients with acute mania.	*Journal of Clinical Psychiatry* 2005; 66(1):111–121. *Journal of Affective Disorders* 2007; 100 (Supp.1):S45–S53.
McIntyre 2005	Quetiapine or haloperidol as monotherapy for bipolar mania.	*European Neuro-psychopharmacology* 2005; 15(5):573–585.
Vieta 2010 Vieta E, et al. Vieta E, et al.	A randomized, placebo and active controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. (quetiapine arm). Randomized, placebo, active controlled study of paliperidone extended-release (ER) for acute manic and mixed episodes in bipolar I disorder. (quetiapine arm).	*Bipolar Disorders* 2010; 12(3):230–243. *European Neuro-psychopharmacology* 2008a; 18(S4):S369.
D1447C00144 Nolen W.	Quetiapine or lithium vs placebo in the maintenance treatment of bipolar disorder (abstract).	*European Neuro-psychopharmacology* 2008; 18(S4):S608.
D144CC00004 Datto C, et al.	Effectiveness of extended-release formulation of quetiapine as monotherapy for the treatment of acute bipolar mania	*European Psychiatry*. 2009; 24:S573.

Asenapine vs placebo (combination therapy)		
A7501009 (Extension A7501008) Calabrese J, et al.	Asenapine as adjunctive treatment for bipolar mania: A placebo-controlled 12 week study and 40 week extension.	*European Psychiatry* 2010a; 25 Supp 1, 1447 PW01-28.
Olanzapine vs placebo (combination therapy)		
Houston 2009 Houston JP, et al.	Olanzapine-divalproex combination versus divalproex monotherapy in the treatment of bipolar mixed episodes.	*Journal of Clinical Psychiatry* 2009; 70 (11):1540–1547.
Houston JP, et al.	Reduced suicidal ideation in bipolar I disorder mixed-episode patients in a placebo-controlled trial of olanzapine combined with lithium or divalproex.	*Journal of Clinical Psychiatry* 2006; 67(8):1246–1252.
Houston JP, et al.	A double-blind, placebo-controlled trial of olanzapine augmentation in bipolar I disorder, mixed episode.	*Biological psychiatry* 2009a; 65(8):131S.
Tohen 2002 Tohen M, et al.	Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially non-responsive to valproate or lithium monotherapy.	*Arch Gen Psychiatry* 2002; 59:62–69.
Baker RW, et al.	Efficacy of olanzapine combined with valproate or lithium in the treatment of dysphoric mania.	*British Journal of Psychiatry 2004;* 185(DEC.):472–478.
Namjoshi MA, et al.	Quality of life assessment in patients with bipolar disorder treated with olanzapine added to lithium or valproic acid.	*Journal of Affective Disorders* 2004; 81(3):223–229.
Tohen 2004	Relapse prevention in bipolar I disorder: 18 month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone.	*British Journal of Psychiatry* 2004; 184: 337–345.
Quetiapine vs placebo (combination therapy)		
Sachs 2004	Quetiapine with lithium or divalproex for the treatment of bipolar mania.	*Bipolar Disorders* 2004; 6(3):213–223.
Suppes 2009	Maintenance treatment for patients with bipolar I disorder.	*American Journal of Psychiatry* 2009; 166(4):476–488.
Vieta 2008	Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder.	*Journal of Affective Disorders* 2008; 109(3):251–263.
Yatham 2007	A double blind, randomized, placebo-controlled trial of quetiapine as an add-on therapy to lithium or divalproex for the treatment of bipolar mania.	*International Clinical Psychopharmacology* 2007; 22(4):212–220.
	Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar	*Journal of Clinical Psychopharmacology*

	mania.	2004; 24(6):599-606.

8. Results of Trials

The results for the direct comparison of asenapine versus olanzapine (monotherapy) and indirect comparison of asenapine versus quetiapine using placebo as common comparator (monotherapy) are shown in the following table. The primary outcome was the difference in change from baseline in Young Mania Rating Scale (YMRS) total score and the key secondary outcomes were the relative risks of being a responder (≥ 50% reduction in YMRS total score) or a remitter (YMRS total score of ≤ 12).

Summary of comparisons, asenapine vs olanzapine or quetiapine as monotherapy

Outcome	Time point	Asenapine vs olanzapine Direct analysis (95% CI)	Asenapine vs quetiapine Indirect analysis (95% CI)
Monotherapy			
LSM Difference in change from baseline YMRS	3 weeks	**2.43 (0.92, 3.93)**	0.51 (-3.02, 2.01)
	12 weeks	-2.80 (-4.55, -1.05)* 1.2 (-0.55, 2.95)**	
	52 weeks	0.4 (-2.45, 3.25)	
Responders (≥ 50% reduction in YMRS)	3 weeks	**RR 0.81 (0.70, 0.94)**	RR 0.93 (0.67, 1.31)
	12 weeks	RR 0.93 (0.84, 1.03)	
	52 weeks	RR 0.97 (0.89, 1.05)	
Remitters (YMRS total score ≤12)	3 weeks	RR 0.88 (0.67, 1.17)	RR 0.90 (0.56, 1.47)
	12 weeks	RR 0.94 (0.85, 1.05)	
	52 weeks	RR 0.97 (0.89, 1.05)	
Difference in change from baseline in CGI-BP severity overall illness	3 weeks	**0.30 (0.12, 0.48)**	0.04 (-0.33, 0.41)
	12 weeks	0.10 (-0.16, 0.36)	
	52 weeks	-0.20 (-0.61, 0.21)	
Difference in change from baseline in CGI-BP severity of mania	3 weeks	**0.25 (0.06, 0.44)**	
	12 weeks	0.10 (-0.14, 0.34)	
	52 weeks	-0.10 (-0.46, 0.26)	
Difference in change from baseline in CGI-BP severity of depression	3 weeks	0.04 (-0.08, 0.17)	
	12 weeks	0.00 (-0.24, 0.24)	
	52 weeks	-0.20 (-0.53, 0.12)	

*Based on adjusted analysis used in error in the submission. ** A corrected analysis conducted during the evaluation.

Asenapine vs. olanzapine (monotherapy)

For monotherapy, at 3 weeks, olanzapine was associated with larger changes from baseline in YMRS total scores than asenapine (the difference was statistically significant but not clinically important, applying a MCID of 3-5 points). Olanzapine was associated with statistically significantly more responders, more remitters (although the difference was not statistically significant), and statistically significantly larger CGI-BP severity of illness and severity of mania score reductions than asenapine treated patients.

The results for the corrected analysis at 12 weeks were consistent with asenapine being non-inferior to olanzapine; there were no statistically significant differences between olanzapine and asenapine at 52 weeks. The analyses at 12 weeks and 52 weeks were based on extension phases of Trials A7501004 and A7501005; the successively smaller proportions of patients entering the continuation trials may suggest some selection biases. Kaplan Meier curves of the time to failure of response in continuation trial A7501007 showed a statistically

significantly longer time to failure of response in patients treated with olanzapine compared to those treated with asenapine (p = 0.0127) at 52 weeks.

Asenapine vs. quetiapine (monotherapy)
While the results numerically favoured quetiapine, there were no statistically significant differences between asenapine and quetiapine at 3 weeks in change from baseline YMRS scores or the secondary outcomes (responders, remitters, changes in CGI-BP scores). However, the indirect comparison of differences in the change from baseline in YMRS total score excluded two quetiapine trials (Bowden 2005, McIntyre 2005) with apparently larger reductions in YMRS. There were no statistically significant differences in change in CGI-BP severity of illness scores between quetiapine and asenapine at 3 weeks. There were no analyses of quetiapine versus asenapine treatment beyond 3 weeks presented in the submission.

Asenapine vs. olanzapine and quetiapine (adjunctive therapy to mood stabilisers)
The results of the indirect comparison of asenapine versus olanzapine and quetiapine in the adjunctive treatment setting are shown in the table below.

Summary of comparisons, asenapine vs olanzapine or quetiapine as adjunctive therapy to mood stabilisers

Outcome	Time point	Asenapine vs olanzapine Indirect analysis (95% CI)	Asenapine vs quetiapine Indirect analysis (95% CI)
Adjunctive therapy to mood stabilisers			
LSM Difference in change from baseline YMRS	6 weeks	0.64 (-2.13, 3.41)	
Responders (≥ 50% reduction in YMRS)	3 weeks		RR 0.94 (0.57, 1.56)
	6 weeks	RR 0.81 (0.53, 1.24)	RR 1.08 (0.75, 1.54)
Remitters (YMRS total score ≤12)	3 weeks		RR 1.08 (0.69, 1.69)
	6 weeks	RR 1.22 (0.87, 1.72)	RR 1.23 (0.84, 1.79)
Difference in change from baseline in CGI-BP improvement	3 weeks		RR 1.08 (0.70, 1.68)
	6 weeks		RR 1.10 (0.75, 1.62)

Overall, outcomes generally numerically favoured olanzapine and quetiapine over asenapine.

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

The PBAC noted that overall, asenapine treated patients appeared to experience more treatment emergent adverse events and serious adverse events compared to olanzapine and quetiapine; particularly headache, dizziness, mania, depression, insomnia, sedation, arthralgia, pain in extremities, nausea, vomiting, anorexia, weight loss and diarrhoea. There was a higher proportion of asenapine treated patients reporting agitation related adverse events and depressive symptoms compared to olanzapine or quetiapine but no analyses of these differences were presented. Asenapine treated patients generally reported less sedation and less weight gain compared to olanzapine treated patients in longer term therapy. The PBAC considered that asenapine is difficult to tolerate in the short-term, highlighted by the range of adverse events experienced in the trials. However, the PBAC noted that asenapine is associated with less weight gain and a better metabolic profile in the longer term compared to olanzapine, which the PBAC considered may represent a potential clinical benefit.

There were statistically significantly more asenapine treated patients withdrawing due to adverse events compared to olanzapine at 3 weeks, but the differences were not statistically significant at 12 and 52 weeks. The extended assessment of comparative harms of asenapine was consistent with the safety profile observed in the randomised trials, and other antipsychotic agents of this class.

The PBAC was concerned that a serious quality use of medicines (QUM) issue exists with regard to the bioavailability of asenapine. The PBAC noted that the bioavailability of the sublingual wafer is 35% when administered sublingually, but drops to less than 2% if it is ingested, and that the intake of water several (2 or 5 minutes) after asenapine administration reduces the bioavailability (to 19 % and 10 % respectively). The PBAC noted the sponsor's advice that both the Product Information and Consumer Medicines Information provide instructions on the correct use of the sublingual formulation. Notwithstanding, the PBAC requested the National Prescribing Service provide comprehensive information for health professionals in view of the serious QUM issues due to the markedly reduced bioavailability of asenapine if it is not administered correctly.

9. Clinical Claim

The submission described asenapine monotherapy as non-inferior in terms of comparative effectiveness over olanzapine monotherapy. This was not accepted by the PBAC.

The submission described asenapine monotherapy as non-inferior in terms of comparative effectiveness over quetiapine monotherapy. The PBAC considered that the results of the indirect comparison of asenapine versus quetiapine supported this claim.

The submission described asenapine as adjunctive therapy to mood stabilisers as non-inferior in terms of comparative effectiveness over olanzapine adjunctive therapy, and non-inferior in terms of comparative effectiveness over quetiapine adjunctive therapy.

The submission described asenapine as non-inferior in terms of comparative safety over olanzapine and quetiapine.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as weighted means of the equi-effective doses derived from the clinical trials in monotherapy and adjunctive therapy to mood stabilisers. They are: asenapine 13.7mg daily and olanzapine 12.9mg mean daily dose, assuming a split of usage between indications of 10% as monotherapy and 90% as adjunctive therapy to mood stabilisers.

The equi-effective doses for the secondary comparator quetiapine were asenapine 16.3 mg and quetiapine 556.9 mg in the monotherapy setting and asenapine 13.4 mg and quetiapine 506.7 mg in the adjunctive setting.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed per year (5 mg and 10 mg combined) was estimated in the submission to be between 10,000 and 50,000 in Year 5, with estimated net savings to the PBS of less than $10 million in Year 5. The financial implications are to be further verified.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended the listing of asenapine sublingual wafers as an Authority Required (STREAMLINED) listing for treatment, for up to 6 months, of an episode of acute mania or mixed episodes associated with bipolar I disorder (as monotherapy or in combination with lithium or sodium valproate) and as monotherapy for maintenance treatment of bipolar I disorder on a cost-minimisation basis with quetiapine. The equi-effective doses are asenapine 16.3 mg and quetiapine 556.9 mg in the monotherapy setting and asenapine 13.4 mg and quetiapine 506.7 mg in the adjunctive setting.

The PBAC agreed that the requested listing for "treatment of bipolar I disorder" was not appropriate, as no data to support use of asenapine in bipolar depression were presented. In addition, the PBAC noted that no comparative analyses beyond 6 weeks were presented for use of asenapine in the adjunctive treatment setting and therefore recommended the restriction should limit use of asenapine to monotherapy only for maintenance treatment.

The PBAC considered that while olanzapine may be an appropriate comparator in clinical practice, it does not have PBS listing for use in the acute treatment setting. Furthermore, the comparison with quetiapine was considered informative as the Committee did not have confidence in the non-inferiority of asenapine and olanzapine, based on the clinical data presented in the submission.

From the pooled results of the direct comparison of asenapine and olanzapine as monotherapy, the PBAC noted that at 3 weeks, olanzapine was associated with a statistically significantly larger change from baseline in Young Mania Rating Scale (YMRS) scores than asenapine (2.43 [95% CI: 0.92, 3.93]), although this was less than the Minimum Clinically Important Difference (MCID) of 4-6 points on YMRS total score previously accepted by the PBAC. Olanzapine was also associated with statistically significantly more responders, remitters (although the difference was not statistically significant), and statistically significantly larger Clinician's Global Impression scale for use in bipolar illness (CGI-BP) severity of illness and severity of mania score reductions than asenapine. At 12 and 52 weeks, there were no statistically significant differences between olanzapine and asenapine.

The PBAC noted that in acute mania, the early phase of treatment is critical. The PBAC considered that the 3-week results of the direct comparison were of most interest and that it could not be concluded from these results that asenapine is non-inferior to olanzapine.

From the results of the indirect comparison of asenapine versus quetiapine as monotherapy using placebo as the common comparator, the PBAC noted there were no statistically significant differences at 3 weeks in change from baseline YMRS scores, responders, remitters or changes in CGI-PB scores, supporting a conclusion that asenapine is most likely to be non-inferior to quetiapine.

In the adjunctive treatment setting, the PBAC noted the results of the indirect comparison of asenapine versus olanzapine and quetiapine showed no statistically significant differences in change from baseline YMRS, or the secondary endpoints. The PBAC noted that no analyses beyond 6 weeks were presented to support the use of asenapine as adjunctive treatment to lithium and sodium valproate in the maintenance treatment of bipolar I disorder.

The PBAC noted that overall, asenapine was associated with more treatment emergent adverse events and serious adverse events compared to olanzapine or quetiapine. However, it was noted that asenapine is associated with less weight gain and a better metabolic profile in the longer term than olanzapine, which the PBAC considered may represent a potential clinical benefit.

The PBAC was concerned that a serious quality use of medicines (QUM) issue exists with regard to the bioavailability of asenapine. The PBAC noted that the bioavailability of the sublingual wafer is 35% when administered sublingually, but drops to less than 2% if it is ingested, and that the intake of water several (2 or 5 minutes) after asenapine administration reduces the bioavailability (to 19 % and 10 % respectively). The PBAC noted the sponsor's advice that both the Product Information and Consumer Medicines Information provide instructions on the correct use of the sublingual formulation. Notwithstanding, the PBAC requested the National Prescribing Service provide comprehensive information for health professionals in view of the serious QUM issues due to the markedly reduced bioavailability of asenapine if it is not administered correctly.

The PBAC considered that the listing of asenapine would provide an additional treatment choice in a stable market and would be unlikely to increase the cost of treating bipolar disease. Listing on a cost-minimisation basis with quetiapine may provide cost savings to the PBS if patients were to switch to asenapine from olanzapine. However, savings would not be realised if patients were to switch from less costly PBS listed drugs.

The PBAC noted the consumer comments received in its consideration of asenapine.

The PBAC recommended that asenapine be included in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements as a shared care model.

Recommendation:
ASENAPINE, sublingual wafer, 5 mg, 10 mg (as maleate)

Restriction: Authority required (STREAMLINED)
Treatment, for up to 6 months, of an episode of acute mania or mixed episodes associated with bipolar I disorder.
Maintenance treatment, as monotherapy, of bipolar I disorder.

Note:
Shared Care Model:
For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.

Maximum quantity: 60
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

The sponsor has no comment.