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 of schizophrenia.

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

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)
Schizophrenia

The PBAC had no objection to the requested wording of the restriction.

5. Clinical Place for the Proposed Therapy

Schizophrenia is a severe psychiatric illness, which is likely to affect seven in every thousand Australians during their lifetime. It is characterised by disturbances in speech, perception, cognition, volition and emotion. Males are more commonly and more severely affected than females. Peak age of onset is in the late teens and early twenties. Atypical antipsychotics are usually used as first-line treatment as they are associated with fewer side effects, although multiple switches between drugs may be required. Clozapine and typical antipsychotics are generally trialled if treatment with several atypical antipsychotics has failed.

The likely place in therapy of asenapine is an alternate treatment option to those agents currently listed on the PBS for treatment of schizophrenia – olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, ziprasidone and paliperidone.

6. Comparator

The submission nominated olanzapine as the main comparator. A secondary comparison with risperidone was also provided. This was accepted by the PBAC.

7. Clinical Trials

The basis of the submission was four randomised head-to-head trials comparing asenapine and olanzapine (Trials 41021, 41022, 25517 and 25543) with three associated unblinded extension studies (Trials 41512, 25520 and 25544) and one direct randomised trial comparing asenapine and risperidone (Trial 41004) with one associated unblinded extension study (Trial 41500).

Only Trial 41004 was published at the time of the submission.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Trials of asenapine versus risperidone (secondary comparator)		
41004 Potkin et al. (2007)	Efficacy and tolerability of asenapine in acute schizophrenia: A placebo- and risperidone-controlled trial.	Journal of Clinical Psychiatry, 68 (10), 1492-1500.

8. Results of Trials

Comparative effectiveness

Asenapine versus olanzapine:

The results of the head-to-head trials of asenapine and olanzapine showed no statistically significant differences in reductions in Positive and Negative Syndrome Scale (PANSS) total scores at 6 weeks, Negative Symptoms Assessment (NSA) total scores at 6 and 26 weeks, PANSS positive scores at 6 weeks, PANSS negative scores at 6 and 26 weeks, Calgary Depression Scale for Schizophrenia (CDSS) scores at 6 weeks and Clinical Global Impression – Severity of Illness (CGI-S) scores at 26 weeks. There were statistically significant differences favouring olanzapine at 26 weeks in PANSS total score, PANSS positive scores, CDSS scores and CGI-S scores, and in PANSS total score at 52 weeks.

The PBAC noted that the differences in PANSS total score were small and did not meet the minimum clinically important difference (MCID) of 7 points, previously accepted by the PBAC. The differences in reductions in CDSS and CGI-S scores were small and unlikely to be clinically important.

There were no statistically significant differences in the proportion of treatment responders (defined as achieving a 30% or greater reduction from baseline in PANSS total score) at 6 weeks between asenapine and olanzapine treated patients. However, there were statistically significantly more treatment responders to olanzapine at 26 and 52 weeks. The response at 6 weeks is patient relevant, particularly for patients with negative symptoms.

The PBAC noted that the rate of discontinuation in the trials was generally higher for patients treated with asenapine than for those treated with olanzapine.

Asenapine versus risperidone

The short-term results of the direct comparison of asenapine and risperidone (Trial 41004) are shown in the table below.

Summary of comparisons of asenapine vs. risperidone for schizophrenia

Outcome	Time point	Asenapine vs risperidone Direct analysis (95% CI) ; p value
Baseline-to-endpoint change in PANSS total score	6 weeks	-4.93 (12.27, 2.41); p = 0.19
Baseline-to-endpoint change in PANSS positive score	6 weeks	-0.35 (-2.83, 2.13); p = 0.78
Baseline-to-endpoint change in PANSS negative score	6 weeks	**-2.16 (-4.18, -0.14)**; **p = 0.04**
Baseline-to-endpoint change in CGI-S score	6 weeks	0.01 (-0.33, 0.35); p = 0.95

Abbreviations: WMD = weighted mean difference; SD = standard deviation; SE = standard error; asen = asenapine; risp = risperidone; PANSS = Positive and Negative Syndrome Scale; CGI-S = Clinical Global Impression - severity of illness.

There were no statistically significant differences between asenapine and risperidone treated patients in changes from baseline in PANSS total score, PANSS positive score and CGI-S score at week 6. There was a statistically significant difference in PANSS negative score favouring asenapine at week 6. However, the difference was small and unlikely to be clinically important.

The proportion of treatment responders (≥ 30% reduction from baseline in PANSS total score) are shown in the table below.

Proportions of treatment responders at 6 weeks (≥ 30% reduction from baseline PANSS total score; ITT, LOCF)

Trial ID	Asenapine		Risperidone		RR (95% CI)
	N	n with events (%)	N	n with events (%)	
41004[a]	58	22 (37.9%)	56	22 (39.3%)	0.97 (0.61, 1.53)

Abbreviations: RR = relative risk; PANSS = Positive and Negative Syndrome Scale.
[a] Recalculated during the evaluation.

There was no statistically significant difference in the proportion of responders in asenapine treated patients compared to risperidone treated patients at week 6.

The consistency of results across changes in PANSS total scores and subscales and responder rates, suggested that asenapine may be considered non-inferior to risperidone. However, Trial 41004 was a small, fixed dose, three arm trial designed to compare asenapine and placebo with risperidone as an active control arm (doses were asenapine 5mg twice daily, risperidone 3mg twice daily). Drop out rates in this small trial were also high.

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

For the comparison of asenapine versus olanzapine, the adverse events most frequently reported by asenapine treated patients were headache, nausea, insomnia, agitation, dyspepsia and sedation. More asenapine treated patients reported symptoms of schizophrenia, anxiety, agitation, depression and akathisia compared to olanzapine treated patients. Patients treated with asenapine also reported statistically significantly less weight gain than patients treated with olanzapine.

Changes from baseline total cholesterol, fasting triglycerides and fasting BSL were more favourable in asenapine treated patients compared to olanzapine treated patients. It is uncertain if the small differences reported are clinically important. There were no significant differences in change from baseline serum low density lipids, HbA1c and prolactin.

For the comparison of asenapine versus risperidone, in Trial 41502 more asenapine treated patients reported symptoms of schizophrenia, and fewer reported weight gain compared to patients treated with risperidone. However, treatment arms were very small.

Overall, the extended assessment of comparative harms of asenapine was consistent with the safety profile observed in the clinical trials, and other antipsychotic agents of this class.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described asenapine monotherapy as non-inferior in terms of comparative effectiveness over olanzapine. Overall, the PBAC was not satisfied that the results of the direct comparison adequately supported this claim.

The submission described asenapine as non-inferior in terms of comparative safety over olanzapine. Asenapine was associated with more anxiety, agitation, depression and akathisia compared to olanzapine, but less weight gain. The PBAC agreed that asenapine is difficult to tolerate in the short-term, highlighted by the range of adverse events experienced in the trials. However, it was noted that asenapine is associated with less weight gain and a better metabolic profile compared to olanzapine.

The submission described asenapine as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over risperidone in the treatment of schizophrenia.

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 extension studies related to the clinical trials. They are: asenapine 14.7 mg daily and olanzapine 13.6 mg mean daily dose (dose relativity 1.08:1).

For the comparison with risperidone, the equi-effective doses derived from the fixed dose short term Trial 41004 were estimated as asenapine 8.3mg and risperidone 5.3mg (dose relativity 1.57:1. The PBAC noted that this comparison with risperidone would represent a lower price compared with the price proposed in the submission versus olanzapine.

11. Estimated PBS Usage and Financial Implications

The number of packs dispensed per year (5 mg and 10 mg combined) was estimated in the submission to be more than 200,000 in Year 5, with estimated net savings per year to the PBS of less than $10 million in Year 5.

The PBAC did not accept the submission's estimated cost savings to the PBS and noted the sponsor's acknowledgement that these savings may not be realised.

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 of schizophrenia on a cost-minimisation basis with risperidone. The equi-effective doses are asenapine 8.3 mg daily and risperidone 5.3 mg daily.

The PBAC accepted that olanzapine was the appropriate comparator based on likely market share, and that risperidone was an appropriate secondary comparator.

From the pooled results of the comparison of asenapine versus olanzapine, the PBAC noted there were no statistically significant differences in the primary efficacy endpoint of change from baseline in Positive and Negative Syndrome Scale (PANSS) total score at 6 weeks, nor were there statistically significant differences in the secondary outcomes of Negative Symptoms Assessment (NSA) total scores at weeks 6 and 26, PANSS positive scores at 6 weeks, PANSS negative scores at 6 and 26 weeks, Calgary Depression Scale Score for Schizophrenia (CDSS) scores at 6 weeks and Clinician Global Impression of Severity (CGI-S) scores at 6 weeks. There were statistically significant differences favouring olanzapine at 26 weeks in PANSS total score, PANSS positive scores, CDSS scores and CGI-S scores, and in PANSS total score at 52 weeks.

The PBAC noted that the differences in PANSS total score were small and did not meet the minimum clinically important difference (MCID) of 7 points, previously accepted by the PBAC.

The PBAC noted that for the proportion of treatment responders (defined as achieving a 30% or greater reduction from baseline in PANSS total score), there were no statistically significant differences between asenapine and olanzapine at 6 weeks. However there were statistically significantly more treatment responders to olanzapine at 26 and 52 weeks.

Overall, the PBAC was not satisfied that the results of the direct comparison adequately supported the claim of non-inferiority of asenapine compared to olanzapine.

From the results of the direct comparison of asenapine versus risperidone from the 6-week Trial 41004, the PBAC noted that there were no statistically significant differences between asenapine and risperidone treated patients in changes from baseline in PANSS total score, PANSS positive score and CGI-S score at week 6. There was a statistically significant difference in PANSS negative score favouring asenapine at week 6. However, the difference was small and unlikely to be clinically important. There were no statistically significant differences in the proportion of responders in asenapine treated patients compared to risperidone treated patients at week 6.

The PBAC acknowledged that there are limited data on which to make a clinical claim against risperidone. However, the PBAC agreed with the ESC that the consistency of results across PANSS total scores and subscales and responder rates from Trial 41004 suggests that

asenapine may be considered non-inferior to risperidone, at least in the short-term. Overall, although there are no longer term data to make a comparison of asenapine with risperidone, the PBAC was more confident about accepting non-inferiority with risperidone because of its lower price

In terms of comparative safety, the PBAC agreed with the ESC that asenapine appears to be difficult to tolerate in the short term. However, it is associated with less weight gain at 6 and 26 weeks and is associated with a better metabolic profile compared to olanzapine, which the PBAC considered may represent a potential clinical benefit.

The PBAC noted that the United States FDA has included asenapine on its list of drugs to monitor due to reports of hypersensitivity reactions, and that this may be consistent with the small number of patients in the clinical trials reporting oropharyngeal swelling and oral hypoaesthesia when taking sublingual asenapine.

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 in its pre-PBAC response 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 did not accept the submission's estimated cost savings to the PBS and noted the sponsor's acknowledgement in its pre-PBAC response that these savings may not be realised. The PBAC further noted that the submission's calculation of the financial implications to the PBS was based on the therapeutic relativity of asenapine to olanzapine of 1.08:1 and that revised estimates of costs will be required based on the therapeutic relativity of asenapine to risperidone of 1.57:1.

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)
Schizophrenia

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.