

asenapine 5mg, 10mg sublingual tablet (Sycrest®)

SMC No. (762/12)

Lundbeck Ltd

10 February 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

asenapine (Sycrest®) is not recommended for use within NHS Scotland.

Indication under review: treatment of moderate to severe manic episodes associated with bipolar I disorder, in adults.

Asenapine when used as monotherapy demonstrated superior efficacy to placebo in reducing manic symptoms as measured using the Young Mania Rating Score at three weeks with maintenance of effect at 12 weeks. In addition, asenapine in combination with lithium or valproate demonstrated superior efficacy to lithium or valproate monotherapy. There are no direct comparative data when asenapine is used as add-on treatment. Indirect comparisons with other second generation antipsychotic agents used as monotherapy and as adjunctive therapy suggested equivalent efficacy.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Treatment of moderate to severe manic episodes associated with bipolar I disorder, in adults.

Dosing Information

The recommended starting dose of asenapine as monotherapy is 10mg twice daily (morning and evening). The dose can be reduced to 5mg twice daily according to clinical assessment. For combination therapy a starting dose of 5mg twice daily is recommended. Depending on the clinical response and tolerability in the individual patient, the dose can be increased to 10mg twice daily. The tablet should be placed under the tongue and allowed to dissolve completely. It should not be chewed or swallowed.

Product availability date

30 January 2012

Summary of evidence on comparative efficacy

Asenapine, which is administered sublingually, is a new antipsychotic whose action is mediated through a combination of antagonist activity at dopamine (D)2 and 5-hydroxytryptamine (5-HT)2A receptors. Actions at other 5-HT and alpha-2-adrenergic receptors, may also contribute to the clinical effects of asenapine. Asenapine has a low oral bioavailability of less than 2%. If it is taken by the correct sublingual route, bioavailability is more than 35%.

Data to support efficacy as monotherapy come from three phase III double-blind, randomised studies in adult patients requiring acute treatment for manic or mixed episodes associated with bipolar I disorder.¹⁻³ Patients were included if their current manic episode had begun ≤ 3 months previously, they had a history of ≥ 1 previous moderate to severe mood episode(s) with or without psychotic features, and had a Young Mania Rating Scale (YMRS) total score ≥ 20 . YMRS is an 11-item clinician-administered instrument, with a total score of 0 to 60, higher scores indicating greater symptom severity. Patients with a primary diagnosis other than bipolar I disorder and those with rapid-cycling bipolar disorder were excluded. In two three-week studies (ARES 3A¹ and ARES 3B²) patients were randomised 2:1:2 to asenapine (10mg sublingually twice daily on day one, and then 5mg to 10mg twice daily thereafter), placebo or olanzapine (15mg orally once daily on day one, and then 5mg to 20mg once daily thereafter). Olanzapine was included as a control to assess assay sensitivity only, as the studies were not powered for a comparison between active drugs. The primary endpoint was the mean change from baseline in the YMRS total score analysed in the intent-to-treat (ITT) population at day 21.

Patients who had successfully completed ARES 3A and ARES 3B were eligible to enter the nine-week double-blind non-inferiority, active comparator extension study (ARES-9).³ Patients receiving asenapine and olanzapine continued treatment, but patients on placebo received blinded asenapine (treatment regimen as for ARES 3A/3B and this group was assessed for safety only). Of the 680 patients who completed the three-week studies, 504 were included in the nine-week extension. The primary endpoint was analysed at week 12 (from baseline of ARES 3A or ARES 3B) in the per-protocol (PP) population using observed case (OC) data and repeated in the ITT population. The non-inferiority of asenapine relative to olanzapine was

established if the upper limit of the 97.5% confidence interval (CI) on the least squares mean difference; (asenapine minus the non-inferiority margin of 4) minus olanzapine was ≤ 0 .

Efficacy data for asenapine used in combination with a mood stabiliser is based on a 12-week placebo-controlled study (APOLLO 12).⁴ This study assessed asenapine as add-on treatment in patients receiving continuous treatment with lithium or valproate for ≥ 2 weeks before screening. Inclusion and exclusion criteria were similar to the monotherapy studies. Patients were randomised equally to asenapine (5mg twice daily on day one, adjustable to 10mg twice daily thereafter) or placebo in addition to their open-label mood stabiliser. The primary endpoint, change from baseline in YMRS total score, was assessed in the ITT population at day 21.

Asenapine was superior to placebo for the primary endpoint in all studies. The non-inferiority of asenapine relative to olanzapine was also demonstrated in ARES-9. The primary efficacy results for all studies are included in the table below.

Table: Primary efficacy endpoint, change from baseline in YMRS total score

	N (ITT or PP)	YMRS at baseline	Least squares (LS) mean YMRS from baseline to endpoint (standard error)	P value
Monotherapy studies				
ARES 3A				
Asenapine	183	29.4	-11.5 (0.8)	p<0.007 (vs. placebo)
Placebo	94	28.3	-7.8 (1.1)	
Olanzapine	203	29.7	-14.6 (0.8)	p<0.0001 (vs. placebo)
ARES 3B				
Asenapine	189	28.3	-10.8 (0.8)	p<0.0001 (vs. placebo)
Placebo	103	29.0	-5.5 (1.0)	
Olanzapine	188	28.6	-12.6 (0.8)	p<0.0001 (vs. placebo)
ARES 9				
PP analysis				
Asenapine	86	29.0	-27.3 (0.64)*	ns versus olanzapine
Olanzapine	128	28.8	-23.7 (0.55)	
ITT analysis				
Asenapine	175	29.0	-20.1 (10.7)	Not reported
Olanzapine	222	28.8	-21.3 (9.6)	
Add-on treatment study				
APOLLO-12				
Asenapine	155	28.0	-10.3 (0.8)	p=0.026 (vs. placebo)
Placebo	163	28.2	-7.9 (0.8)	

*After adjustment for the non-inferiority margin of -4.

Primary endpoint was assessed at day 21 for ARES 3A and ARES 3B, at week 12 for ARES 9, and day 21 for APOLLO-12.

Secondary endpoints included YMRS responders ($\geq 50\%$ reduction in YMRS total score), YMRS remitters (patients with YMRS total score ≤ 12) and change from baseline in Clinical Global Impression for Bipolar disorder (CGI-BP).

The percentage of responders and remitters in the asenapine group were not significantly different from placebo in the ARES-3A study but were significant in ARES 3B. In both studies, there were significant differences for olanzapine versus placebo for responders and remitters.

Changes from baseline in CGI-BP mania severity were superior for asenapine and olanzapine versus placebo.

In ARES 9 there was no significant difference between the active treatments for YMRS responders and remitters or for change CGI-BP (mania, depression and overall bipolar illness). There were no significant differences between asenapine and olanzapine at week 12 in quality of life measured using the Short Form 36 questionnaire.

In the APOLLO 12 study, at week 12, the LS mean change in YMRS total score from baseline to week 12 was -12.7 (SE 0.9) for asenapine and -9.3 (0.9) for placebo, asenapine had significantly higher YMRS responder and remitter rates than placebo and the change from baseline for CGI-BP (mania and overall bipolar illness severities) was higher with asenapine than with placebo. Of the 116 patients who completed APOLLO 12, 77 patients enrolled into a 40-week double-blind extension where patients continued with the treatment previously allocated. The mean change in YMRS total score from primary study baseline at week 52 was -17.2 for asenapine (n=38) and -19.7 for placebo (n=33).

Summary of evidence on comparative safety

In the comparative 12-week study, treatment-emergent adverse events (AE) occurred in approximately 77% of patients and treatment-related AE occurred in 65% (117/181), 64% (146/229) and 53% (52/94) of patients on asenapine, olanzapine and placebo/asenapine respectively. Most AE were mild to moderate in intensity. Serious treatment-related AE occurred in 2.8% (5/181), 3.5% (8/229) and 4.3% (4/94) of patients on asenapine, olanzapine and placebo/asenapine respectively.

AE that occurred in a higher proportion of asenapine treated than olanzapine treated patients included dizziness (13% versus 6.6%), insomnia (13% versus 10%), nausea (8.3% versus 3.1%). Conversely, sedation (14% versus 18%), headache (12% versus 15%), weight gain (7.4% versus 14%) and dry mouth (3.9% versus 11%) occurred in a lower proportion of asenapine than olanzapine treated patients. Mean change in weight \pm SD was 1.9kg \pm 3.92 on asenapine, 4.1kg \pm 5.11 on olanzapine and 0.5kg \pm 3.51 on placebo/asenapine. The percentage of patients with a clinically significant weight gain was 19% for asenapine treated patients versus 31% for olanzapine treated patients. Weight gain/increased appetite is listed as a common adverse drug reaction in the summary of product characteristics (SPC). The incidence of extrapyramidal symptoms (any type) was 15% on asenapine, 13% on olanzapine and 10% on placebo.

In the two open extension studies of ARES-9 and APOLLO-12, no additional safety concerns were reported after 52 weeks treatment, although patient numbers were small.

Summary of clinical effectiveness issues

Bipolar I disorder is a chronic, typically cyclical, mood disorder. Four phase III studies (three in monotherapy and one as add-on therapy to lithium or valproate) in patients requiring treatment for acute manic or mixed episodes associated with bipolar I disorder, demonstrated that asenapine was superior to placebo for the primary endpoint, change in YMRS. One study (ARES 9) included an active comparator, olanzapine, and using the pre-defined statistical methodology, the non-inferiority of asenapine versus olanzapine was demonstrated at week 12. Clinically significant weight gain was lower for asenapine than olanzapine treated patients. However, the study design and methodology were criticised by the European Medicines Agency (EMA) because patients were required to have completed the three-week ARES 3A or ARES 3B studies (where more patients discontinued in the asenapine groups than the olanzapine groups) to be eligible for ARES 9 and re-randomisation was not undertaken.⁶ The EMA requested an additional analysis that included all patients recruited to ARES 3A and ARES 3B. The EMA were satisfied that although non-inferiority for olanzapine could not be included, the overall data were supportive of the maintenance of the effect of asenapine during the episode.

There were also limitations with respect to other efficacy data. In the placebo-controlled study of asenapine as add-on treatment (APOLLO 12), discontinuations were high for both groups. Asenapine was superior to placebo for change in YMRS at week 3 (primary endpoint). However for the secondary endpoints of change in YMRS at week 52 and percentage of responders and remitters there were numerically better outcomes for placebo. Furthermore in ARES 3A there were no significant differences for asenapine versus placebo for the secondary endpoints of percentage of YMRS responders and YMRS remitters. However, the studies were not powered to detect a difference in these secondary endpoints.

The only available direct comparative data is versus olanzapine as monotherapy treatment. The submitting company included indirect comparisons (Bucher methodology) for asenapine versus comparators in monotherapy (over 12 weeks) and as an adjunct to mood stabilisers (over 6 weeks). These indicate that asenapine has similar efficacy to olanzapine, quetiapine and aripiprazole in terms of change from baseline in the YMRS total score. Only selected AE were reported for the indirect comparison. For these adverse event results, it was shown that asenapine, quetiapine, aripiprazole and olanzapine were similar. Results of a mixed treatment comparison, conducted in monotherapy treatment only, were also provided by the submitting company. These showed that asenapine has similar efficacy to quetiapine, aripiprazole and olanzapine as well as lithium, haloperidol and risperidone. Results of a multiple treatments meta-analysis of anti-manic drugs in acute mania, which assessed outcomes at three weeks, have recently been published⁷ and, in general, support the indirect comparisons provided by the submitting company. However, the authors of this meta-analysis considered that haloperidol, risperidone, and olanzapine were among the most effective treatments, and olanzapine, risperidone, and quetiapine were better than the other drugs in terms of acceptability (measured as treatment discontinuation). Three week follow-up would be insufficient to identify differences in adverse effect profiles.

The EMA raised concerns that the optimal dosing regimen for asenapine had not been established for bipolar I disorder and a dose finding study is to be conducted as part of a post-approval commitment.

Due to asenapine's low oral bioavailability patients need to follow the administration instructions carefully to obtain the optimum dose. Other atypical antipsychotics have the advantage of being available in a variety of formulations.

SMC clinical experts indicated that a range of antipsychotics are currently used in the treatment of acute manic episodes including olanzapine, haloperidol and risperidone.

Summary of comparative health economic evidence

The submitting company conducted two cost-minimisation analyses comparing asenapine with olanzapine, quetiapine and aripiprazole, (1) as monotherapy, or (2) as adjunctive therapy with a mood stabilizer, lithium or sodium valproate, for the treatment of moderate to severe manic episodes associated with bipolar 1 disorder in adults. The base case time horizon was 12 weeks for the asenapine monotherapy analysis and 6 weeks for the asenapine adjunctive therapy analysis.

The clinical evidence for the comparable efficacy of asenapine versus olanzapine monotherapy was derived from a phase III randomised, double-blind, double dummy study in adults with acute manic/mixed episode associated with bipolar I disorder. There were no head-to-head trials comparing asenapine monotherapy to quetiapine, or aripiprazole monotherapy, or comparing asenapine adjunctive therapy to olanzapine, quetiapine or aripiprazole adjunctive therapy. As such an indirect comparison was used to support the economic analyses.

The analyses compared the treatment costs of asenapine and the comparator antipsychotics, and included the costs associated with switching treatment because of adverse events, which were assumed to differ between asenapine and the comparators.

The results of the monotherapy analysis showed the incremental costs associated with 12 weeks of asenapine versus each of the comparator antipsychotics to be -£63, -£162 and -£249 per patient for olanzapine, quetiapine and aripiprazole, respectively. The results of the adjunctive therapy analysis showed the incremental costs associated with 6 weeks of asenapine versus each of the comparator antipsychotics to be -£19, -£52 and -£135 per patient for olanzapine, quetiapine and aripiprazole, respectively. Asenapine would therefore be associated with cost savings and would be the preferred treatment on cost-minimisation grounds in both analyses, with the main driver of the savings being the lower drug-related costs.

The key finding from the sensitivity analyses was that there would be small additional costs associated with asenapine compared to olanzapine when the WHO defined daily doses, rather than the mean doses from the studies were applied. Asenapine would therefore no longer be the preferred treatment on cost-minimisation grounds.

The main limitations of the analysis were:

- SMC clinical experts have advised that risperidone and haloperidol are also current treatment options in NHS Scotland but these were not included as comparator treatments within the submission. Aripiprazole has been not recommended by SMC for use in this indication.
- For a cost-minimisation analysis to be the appropriate choice of evaluation, all relevant outcomes should be equivalent. This should extend to there being no differences in adverse events between treatments; however, the submitting company has included such differences in their analyses, with the result being differential costs associated with switching treatments. The company provided revised analysis to show the impact of excluding the costs associated with switching treatments due to adverse events. The results indicated that asenapine was still cost-saving against the base case comparator treatments.

Olanzapine has recently become available in NHS Scotland as a generic medicine but the base case analysis did not take account of this. The submitting company was asked to provide additional analysis using selected generic prices. The results showed that when the lowest generic olanzapine price or Scottish Tariff price is applied, asenapine as monotherapy or as adjunctive therapy would no longer be preferred on cost-minimisation grounds. When the highest generic olanzapine price is applied, asenapine as adjunctive therapy would no longer be preferred on cost minimization grounds, but asenapine monotherapy would be associated with cost savings and would therefore be preferred on cost minimization grounds.

The submitting company subsequently requested that SMC consider asenapine for use only in those patients for whom either generic olanzapine or risperidone are not considered the most appropriate option.

The committee had concerns about the robustness of the cost-minimisation analysis submitted as cost-effectiveness relative to olanzapine was not demonstrated. The company also failed to adequately consider the cost-effectiveness of asenapine relative to the other antipsychotics that would be displaced in practice, risperidone and haloperidol.

Given these issues, the economic case was considered not to have been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was received from Bipolar Scotland.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published SIGN 82; Bipolar affective disorder in May 2005.

It recommended the following for the treatment of acute mania;

- Acute manic episodes should be treated with oral administration of an antipsychotic drug or semisodium valproate.
- Lithium can be used if immediate control of overactive or dangerous behaviour is not needed or otherwise should be used in combination with an antipsychotic.

The following good practice points are also included;

- Intramuscular injection of antipsychotics and/or benzodiazepines (lorazepam) should be used in emergency situations, in accordance with local protocols.
- Benzodiazepines may be used as adjunctive treatment in acute mania where sedation is a priority.
- Patients who suffer an acute manic episode whilst on maintenance treatment with an antimanic drug should have their dose of antimanic drug optimised. Treatment with an antipsychotic or valproic acid should be initiated as appropriate.
- Severe, treatment-resistant mania may require electroconvulsive treatment to avert harm due to the illness.
- Combination therapy with several antimanic agents from different classes may be required in treatment resistant cases.
- Duration of treatment will be determined by the reduction of symptoms, the emergence of side effects and the need to provide treatment for residual symptoms and prevent relapse
- Antidepressant drug treatment should be reduced and discontinued during an acute manic episode
- A clear terminology should be implemented to avoid confusion in the prescription of sodium valproate and semisodium valproate, as well as the different lithium salts and preparations.

The National Institute for Health and Clinical Excellence (NICE) issued clinical guideline 38; Bipolar disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care in July 2006.

It recommends the following:

If a patient develops acute mania when not taking antimanic medication, treatment options include starting an antipsychotic, valproate or lithium. When making the choice, prescribers should take into account preferences for future prophylactic use, the side-effect profile, and consider:

- prescribing an antipsychotic if there are severe manic symptoms or marked behavioural disturbance as part of the syndrome of mania
- prescribing valproate or lithium if symptoms have responded to these drugs before, and the person has shown good compliance
- avoiding valproate in women of child-bearing potential
- using lithium only if symptoms are not severe because it has a slower onset of action than antipsychotics and valproate.

If treating acute mania with antipsychotics, olanzapine, quetiapine or risperidone should normally be used, and the following should be taken into account:

- individual risk factors for side effects (such as the risk of diabetes)
- the need to initiate treatment at the lower end of the therapeutic dose range recommended in the summary of product characteristics and titrate according to response
- that if an antipsychotic proves ineffective, augmenting it with valproate or lithium should be considered
- that older people are at greater risk of sudden onset of depressive symptoms after recovery from a manic episode.

Additional information: comparators

Other second generation atypical antipsychotic drugs and haloperidol. Aripiprazole is not recommended by SMC for treating moderate to severe manic episodes in bipolar 1 disorder or for preventing new manic episodes.

Cost of relevant comparators

Drug	Dose Regimen	Cost per 28 days (£)
asenapine	5mg to 10mg sublingually twice daily	96
quetiapine	200mg to 400mg twice daily	106 to 211
aripiprazole	15mg to 30mg orally once daily	96 to 191
olanzapine (Zyprexa®)	10mg to 20mg orally once daily	87 to 159
olanzapine (generic)	10mg to 20mg orally once daily	9 to 17
risperidone	1mg to 6mg orally once daily	1.58 to 23
haloperidol	up to 5mg orally three times daily	7

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 22 November 2011 and 21 December 2011. NB: SIGN guideline 82 recommends that the duration of treatment should be determined by the reduction of symptoms, the emergence of side effects and the need to provide treatment for residual symptoms and prevent relapse

Additional information: budget impact

The submitting company estimated the population eligible for treatment in the proposed positioning to be 249 patients in year 1, rising to 899 by year 5. Based on market share estimates of 4.1% in year 1, rising to 15% in year 5, and a 50% discontinuation rate, the impact on the medicines budget impact was estimated at £324k in year 1 and £1.16m in year 5. The net medicines budget impact was estimated at -£244k in year 1 and -£52k in year 5.

The estimated budget impact showed a smaller net cost saving in year 5 as the result of displaced medicines becoming generic and costing less in the future.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J Affect Disord* 2010;122(1-2):27-38.
2. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar Disord* 2009;11(7):673-86.
3. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine versus olanzapine in acute mania: a double-blind extension study. *Bipolar Disord* 2009;11(8):815-26.
4. Calabrese JR, Stet, L., Kothari, H., et al. Asenapine as adjunctive treatment for bipolar mania: results of a placebo-controlled 12-week study and 40-week extension. Boston, USA: Poster presented at the 62nd Institute on Psychiatric Services of the American Psychiatric Association (APA), 2010.
5. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. *J Affect Disord* 2010;126(3):358-65
6. European Medicines Agency. Public assessment report for Sycrest (asenapine) Procedure No. EMEA/H/C/001177
7. Cipriani A, Barbui C, Salanti G et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *The Lancet* 2011; 378: 1306-15

This assessment is based on data submitted by the applicant company up to and including 05 March 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.