Asenapine (Sycrest) for the treatment of acute mania

DTC decision: Restricted Medicine
The Drugs and Therapeutics Committee has added asenapine to the list of medicines which it considers as restricted for use with the Trust. The decision was based on the limited efficacy and safety data. Whether it offers any advantages over established, more cost-effective alternatives is unclear. It may offer a treatment option in people with swallowing difficulties.

Clinicians wishing to prescribe asenapine should complete a restricted medicine request form that details why other established antipsychotics are not suitable. Asenapine will not be prescribed in primary care as it is currently black listed by Oxfordshire and Buckinghamshire PCTs.

For further detailed information please see below.

Key Points
- Asenapine is an antipsychotic licensed for the treatment of acute mania as monotherapy or as add-on treatment to existing mood stabiliser therapy.
- It is not licensed for relapse prevention and has not been assessed for efficacy in bipolar depression.
- Asenapine is a sublingual tablet with strict administration instructions which may limit the patient group in whom it can be used.
- Efficacy has been demonstrated in 3 monotherapy studies and one add-on study.
- Comparisons with antipsychotics other than olanzapine in mania are lacking.
- A recent multiple treatments meta-analysis comparing the efficacy and acceptability of antimanic drugs in acute mania ranked asenapine as less effective and less acceptable (based on drop out rates) than other antipsychotics (haloperidol, risperidone, olanzapine, quetiapine and aripiprazole).
- Efficacy and safety data beyond 52 weeks are limited. Rare adverse events may not yet have been determined.
- Asenapine commonly causes somnolence and anxiety may cause more EPS than olanzapine and risperidone (but less than haloperidol). It may cause less weight gain than olanzapine but appears to have similar changes in metabolic variables.
- It is a black triangle drug that is intensively monitored to ensure that any new safety hazards are identified promptly.
- Asenapine is significantly more expensive than generically available olanzapine and risperidone (and soon to be available generic quetiapine IR and XL) but cheaper than aripiprazole.
- Asenapine may be useful when other established antipsychotics are relatively contraindicated but due to the relative lack of efficacy and safety data it should be used cautiously. It may also be useful in patients with swallowing difficulties.

Asenapine (Sycrest) is indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults as monotherapy or as add-on therapy with a mood stabiliser. The European Commission granted a marketing authorisation valid throughout the European Union on 1 September 2010 and it was launched in the UK on 1 January 2012.

Pharmacology
Asenapine is an antagonist of serotonin, noradrenaline, dopamine and histamine receptors. Like other second-generation antipsychotics it has a high 5HT2a/D2 binding affinity ratio. The mechanism of action of asenapine, as with other
medicinal products having efficacy in bipolar disorder, is not fully understood. However, based on its receptor pharmacology, it is proposed that the efficacy of asenapine is mediated through a combination of antagonist activity at D2 and 5-HT2A receptors. Actions at other receptors e.g., 5-HT1A, 5-HT1B, 5-HT2C, 5-HT6, 5-HT7, D3, and α2-adrenergic receptors, may also contribute to the clinical effects of asenapine.¹

**Pharmacokinetics** ¹

**Absorption:** Following sublingual administration, asenapine is rapidly absorbed with peak plasma concentrations occurring within 0.5 to 1.5 hours. The absolute bioavailability of sublingual asenapine at 5 mg is 35%. The absolute bioavailability of asenapine when swallowed is low (<2% with an oral tablet formulation). The intake of water several (2 or 5) minutes after asenapine administration resulted in decreased (19% and 10% respectively) asenapine exposure. Therefore, eating and drinking should be avoided for 10 minutes after administration.

Increasing the dose from 5 to 10 mg twice daily (a two-fold increase) results in less than linear (1.7 times) increases in both the extent of exposure and maximum concentration. The less than proportional increase of Cmax and AUC with dose may be attributed to limitations in the absorption capacity from the oral mucosa following sublingual administration.

**Metabolism:** Asenapine is extensively metabolised. Direct glucuronidation (mediated by UGT1A4) and cytochrome P450 (primarily CYP1A2, with contributions of 2D6 and 3A4) mediated oxidation and demethylation are the primary metabolic pathways for asenapine. Asenapine is a weak inhibitor of CYP2D6. Asenapine does not induce CYP1A2 or CYP3A4 enzymes. Metabolites have no significant clinical activity.³

**Dose**¹

The recommended starting dose of Sycrest as monotherapy is 10 mg twice daily. One dose should be taken in the morning and one dose should be taken in the evening. The dose can be reduced to 5 mg twice daily according to clinical assessment. For combination therapy a starting dose of 5 mg twice daily is recommended. Depending on the clinical response and tolerability in the individual patient, the dose can be increased to 10 mg twice daily.

The European Medicines Agency (EMA) has raised concerns that the optimal dosing regimen for asenapine had not been established for bipolar I disorder. A dose finding study is to be conducted as part of a post-approval commitment.⁴

**Special patient populations**

- **Paediatric population** – Asenapine is not licensed for use in <18 year olds as safety and efficacy have not been established.
- **Elderly patients** - Limited data on efficacy in patients 65 years of age and older are available therefore asenapine should be used with care in the elderly.
- **Renally impaired patients** - No dose adjustment is required for patients with renal impairment. There is no experience with asenapine in severe renal impairment (patients with a creatinine clearance less than 15 ml/min).
- **Hepatic impaired patients** - No dose adjustment is required for patients with mild hepatic impairment. The possibility of elevated asenapine plasma levels cannot be excluded in some patients with moderate hepatic impairment (Child-Pugh B) and caution is advised. In subjects with severe hepatic impairment (Child-Pugh C), a 7-fold increase in asenapine exposure was observed. Sycrest is therefore not recommended in patients with severe hepatic impairment.

**Formulation**¹

Sublingual tablets in 5mg and 10mg strengths supplied in peelable blisters.

**Administration**¹

Asenapine tablets should be removed from the packaging with dry hands and placed under the tongue where it will dissolve within a few seconds. No food or drink should be consumed for 10 minutes after administration. If other medicines are taken at the same time, asenapine should be taken last.

**Buccal and sublingual administration:**

A pharmacokinetic study has been conducted to determine the effect of allowing the tablet to dissolve buccally (between the gum and cheek) or on the top of the tongue (supralingual). This was a 3 way cross-over study in 36 men who received 5mg via sublingual, supralingual and buccal routes at least a week apart. Buccal and sublingual routes were not
bioequivalent (AUC and Cmax were higher with buccal – 24% higher exposure) however the authors judged this to be of limited clinical relevance. Bioequivalence with the supralingual route was established based on AUC (6% lower). 5 Buccal and supralingual routes of administration are not covered by the terms of the product licence.

Adverse Effects

Asenapine has been directly compared with olanzapine in mania studies and with risperidone and haloperidol in schizophrenia studies. It causes the typical range of antipsychotic adverse effects including sedation and dose-dependent extrapyramidal symptoms (EPS). There is a higher incidence of EPS than olanzapine and risperidone but a lower incidence than haloperidol. 6 Asenapine caused small increases in QTc interval prolongation in a QT study, but not increased rates of clinically relevant QT prolongation in clinical trials. It may cause orthostatic hypotension in some people particularly early in treatment. 6 Somnolence and anxiety are reported very commonly (>10%). 1 Trials indicate a lower incidence of weight gain with asenapine than olanzapine but changes in metabolic variables were similar. 7 The incidence of weight gain was similar to that of haloperidol. 6 Asenapine may cause less antimuscarinic effects and hyperprolactinaemia than some other antipsychotics. 6

Oral hypoesthesia is a common (1-10%) adverse effect and patients should be advised that the anaesthetic effect of the tablet on the mouth and tongue is nothing to be concerned about and usually resolves within an hour. 6, 8

Interactions 1

Co-administration with fluvoxamine (a strong CYP1A2 inhibitor) may result in increased asenapine levels.

Co-administration with paroxetine (a CYP2D6 substrate and inhibitor) may result in increased paroxetine levels.

Asenapine may enhance the inhibitory effects of paroxetine on its own metabolism.

Because of its α1-adrenergic antagonism with potential for inducing orthostatic hypotension, asenapine may enhance the effects of certain antihypertensive agents.

Place in therapy

Asenapine should not be considered as a first-line treatment option. A recent multiple treatments meta-analysis comparing the efficacy and acceptability of antimanic drugs in acute mania ranked asenapine as less effective and less acceptable (based on drop out rates) than other antipsychotics (haloperidol, risperidone, olanzapine, quetiapine and aripiprazole). 3, 5, 9, 3 The relative lack of efficacy and safety data and the lack of direct comparative studies with antipsychotics other than olanzapine suggests that asenapine should be used cautiously until further studies are available. It may, however, be useful when other established antipsychotics are relatively contraindicated. When selecting treatments for acute mania, longer term treatment options are also usually being considered. As asenapine does not have a licence for relapse prevention this should be taken into account in the decision process.

References

3) Progress reports Advances in bipolar I disorder: a clinical review of asenapine. Report from a symposium at the British Association for Psychopharmacology meeting, Harrogate, 25 July 2011
8) Lundbeck Limited. How to take your Sycrest tablets Date of preparation October 2011

Other references: