SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sycrest 5 mg sublingual tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 5 mg asenapine (as maleate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual tablet
5 mg: Round, white to off-white, sublingual tablets debossed with “5” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sycrest is indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.

4.2 Posology and method of administration

Posology

The recommended starting dose of Sycrest as monotherapy is 5 mg twice daily. One dose should be taken in the morning and one dose should be taken in the evening. The dose can be increased to 10 mg twice daily based on individual clinical response and tolerability. See section 5.1. 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.

Special populations

Elderly
Sycrest should be used with care in the elderly. Limited data on efficacy in patients 65 years of age and older are available. Available pharmacokinetic data are described in section 5.2.

Renal impairment
No dose adjustment is required for patients with renal impairment. There is no experience with asenapine in patients with severe renal impairment who have a creatinine clearance less than 15 mL/min.

Hepatic impairment
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. Thus, Sycrest is not recommended in patients with severe hepatic impairment.

Paediatric population
A pharmacokinetic study and a short term efficacy and safety study were performed in a paediatric population (ages 10-17 years) with manic or mixed episodes associated with bipolar I disorder. Long term safety in this population was explored in a 50-week, open-label, uncontrolled extension study. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

The tablet should not be removed from the blister until ready to take it. Dry hands should be used when touching the tablet. The tablet should not be pushed through the tablet pack. The tablet pack should not be cut or torn. The coloured tab should be peeled back and the tablet should be removed gently. The tablet should not be crushed.

To ensure optimal absorption, the Sycrest sublingual tablet should be placed under the tongue and allowed to dissolve completely. The tablet will dissolve in saliva within seconds. Sycrest sublingual tablets should not be chewed or swallowed. Eating and drinking should be avoided for 10 minutes after administration.

When used in combination with other medicinal products, Sycrest should be taken last.

Treatment with Sycrest is not advised in patients who are unable to comply with this method of administration, as the bioavailability of asenapine when swallowed is low (< 2 % with an oral tablet formulation).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Elderly patients with dementia-related psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic substances are at an increased risk of death.

Sycrest is not approved for the treatment of patients with dementia-related psychosis and is not recommended for use in this particular group of patients.

Neuroleptic malignant syndrome
Neuroleptic malignant syndrome (NMS), characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported to occur with antipsychotics, including asenapine. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure.
If a patient develops signs and symptoms indicative of NMS Sycrest must be discontinued.

Seizures
In clinical trials, cases of seizure were occasionally reported during treatment with asenapine. Therefore, Sycrest should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

Suicide
The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder and close supervision of high-risk patients should accompany treatment.

Orthostatic hypotension

Asenapine may induce orthostatic hypotension and syncope, especially early in treatment, probably reflecting its α1-adrenergic antagonist properties. Elderly patients are particularly at risk for experiencing orthostatic hypotension (see section 4.8). In clinical trials, cases of syncope were occasionally reported during treatment with Sycrest. Sycrest should be used with caution in elderly patients and in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration and hypovolemia).

Tardive dyskinesia
Medicinal products with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical, involuntary movements, predominantly of the tongue and/or face. In clinical trials, cases of tardive dyskinesia were occasionally reported during treatment with asenapine. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on Sycrest, discontinuation of treatment should be considered.

Hyperprolactinaemia
Increases in prolactin levels were observed in some patients with Sycrest. In clinical trials, there were few adverse reactions related to abnormal prolactin levels reported.

QT interval
Clinically relevant QT prolongation does not appear to be associated with asenapine. Caution should be exercised when Sycrest is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QT interval.

Hyperglycaemia and diabetes mellitus
Hyperglycaemia or exacerbation of pre-existing diabetes has occasionally been reported during treatment with asenapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia or bipolar disorder and the increasing incidence of diabetes mellitus in the general population. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic treatment. Cases of dysphagia were occasionally reported in patients treated with Sycrest.

Body temperature regulation
Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic medicinal products. From the clinical trials, it is

concluded that clinically relevant body temperature dysregulation does not appear to be associated with asenapine. Appropriate care is advised when prescribing Sycrest for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant medicinal products with anticholinergic activity or being subject to dehydration.

Patients with severe hepatic impairment
Asenapine exposure is increased 7-fold in patients with severe hepatic impairment (Child-Pugh C). Therefore, Sycrest is not recommended in such patients.

Parkinson's disease and dementia with Lewy bodies
Physicians should weigh the risks versus the benefits when prescribing Sycrest to patients with Parkinson's disease or dementia with Lewy Bodies (DLB) since both groups may be at increased risk of neuroleptic malignant syndrome as well as having an increased sensitivity to antipsychotics. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Falls
Asenapine may cause adverse effects such as somnolence, orthostatic hypotension, dizziness and extrapyramidal symptoms, which may lead to falls and, consequently, fractures or other injuries. Patients at risk for fall should be evaluated prior to prescribing asenapine.

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary effects of asenapine on the central nervous system (CNS) (see section 4.8), caution should be used when it is taken in combination with other centrally acting medicinal products. Patients should be advised to avoid alcohol while taking Sycrest.

Potential for other medicinal products to affect Sycrest
Asenapine is cleared primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2). The potential effects of inhibitors and an inducer of several of these enzyme pathways on asenapine pharmacokinetics were studied, specifically fluvoxamine (CYP1A2 inhibitor), paroxetine (CYP2D6 inhibitor), imipramine (CYP1A2/2C19/3A4 inhibitor), cimetidine (CYP3A4/2D6/1A2 inhibitor), carbamazepine (CYP3A4/1A2 inducer) and valproate (UGT inhibitor). Except for fluvoxamine, none of the interacting medicinal products resulted in clinically relevant alterations in asenapine pharmacokinetics.

During combined administration with a single dose of asenapine 5 mg, fluvoxamine 25 mg twice daily resulted in a 29 % increase in asenapine AUC. The full therapeutic

dose of fluvoxamine would be expected to produce a greater increase in asenapine plasma concentrations. Therefore, co-administration of asenapine and fluvoxamine should be approached with caution.

Potential for Sycrest to affect other medicinal products
Because of its α1-adrenergic antagonism with potential for inducing orthostatic hypotension (see section 4.4), Sycrest may enhance the effects of certain antihypertensive agents.

Asenapine may antagonise the effect of levodopa and dopamine agonists. If this combination is deemed necessary, the lowest effective dose of each treatment should be prescribed.

In vitro studies indicate that asenapine weakly inhibits CYP2D6. Clinical drug interaction studies investigating the effects of CYP2D6 inhibition by asenapine showed the following results:

- Following co-administration of dextromethorphan and asenapine in healthy subjects, the ratio of dextrorphan/dextromethorphan (DX/DM) as a marker of CYP2D6 activity was measured. Indicative of CYP2D6 inhibition, treatment with asenapine 5 mg twice daily resulted in a fractional decrease in DX/DM ratio to 0.43. In the same study, treatment with paroxetine 20 mg daily decreased the DX/DM ratio to 0.032.

- In a separate study, co-administration of a single 75 mg dose of imipramine with a single 5 mg dose of asenapine did not affect the plasma concentrations of the metabolite desipramine (a CYP2D6 substrate).

- Co-administration of a single 20 mg dose of paroxetine (a CYP2D6 substrate and inhibitor) during treatment with 5 mg asenapine twice daily in 15 healthy male subjects resulted in an almost 2-fold increase in paroxetine exposure.

In vivo asenapine appears to be at most a weak inhibitor of CYP2D6. However, asenapine may enhance the inhibitory effects of paroxetine on its own metabolism.
Therefore, Sycrest should be co-administered cautiously with medicinal products that are both substrates and inhibitors for CYP2D6.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Sycrest in pregnant women. Asenapine was not teratogenic in animal studies. Maternal and embryo toxic effects were found in animal studies (see section 5.3).

Newborn infants exposed to antipsychotics (including Sycrest) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder in newborn infants. Consequently, newborn infants should be monitored carefully.

Sycrest should not be used during pregnancy unless the clinical condition of the woman requires treatment with asenapine and only if the potential benefit outweighs the potential risk to the foetus.

Breast-feeding
Asenapine was excreted in milk of rats during lactation. It is not known whether asenapine or its metabolites are excreted in human milk. Breast-feeding should be discontinued during treatment with Sycrest.

Fertility
No impairment of fertility has been observed in nonclinical studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Asenapine may cause somnolence and sedation. Therefore, patients should be cautioned about driving and using machines until they are reasonably certain that Sycrest therapy does not affect them adversely.

4.8 Undesirable effects

Summary of safety profile
The most frequently reported adverse drug reactions (ADRs) associated with the use of asenapine in clinical trials were somnolence and anxiety. Serious hypersensitivity reactions have been reported. Other serious ADRs are discussed in more detail in section 4.4.

Tabulated list of adverse reactions
The incidences of the ADRs associated with asenapine therapy are tabulated below. The table is based on adverse reactions reported during clinical trials and/or post-marketing use.

All ADRs are listed by system organ class and frequency; very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), and not known (cannot be estimated from the available data). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic disorders				Neutropenia	
Immune system disorders			Allergic reactions		
Metabolism and nutrition disorders		Weight increased Increased appetite	Hyperglycaemia		
Psychiatric disorders	Anxiety				
Nervous system disorders	Somnolence	Dystonia Akathisia Dyskinesia Parkinsonism Sedation Dizziness Dysgeusia	Syncope Seizure Extrapyramidal disorder Dysarthria Restless legs syndrome	Neuroleptic malignant syndrome	
Eye disorders				Accommodation disorder	
Cardiac disorders			Sinus bradycardia Bundle branch block Electrocardio-gram QT prolonged Sinus tachycardia		
Vascular disorders			Orthostatic hypotension Hypotension		
Respiratory, thoracic and mediastinal disorders				Pulmonary embolism	
Gastrointestinal disorders		Hypoaesthesia oral Nausea Salivary hypersecretion	Swollen tongue Dysphagia Glossodynia Paraesthesia oral Oral mucosal lesions (ulcerations,		

			blistering and inflammation)		
Hepatobiliary disorders		Alanine aminotransferase increased			
Injury, poisoning and procedural complications					Falls*
Musculoskeletal and connective tissue disorders		Muscle rigidity		Rhabdomyolysis	
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal (see 4.6)
Reproductive system and breast disorders			Sexual dysfunction Amenorrhoea	Gynaecomastia Galactorrhoea	
General disorders and administration site conditions		Fatigue			

* See subsection "*Falls*" below

Description of selected adverse reactions

Extrapyramidal Symptoms (EPS)
In clinical trials, the incidence of extrapyramidal symptoms in asenapine-treated patients was higher than placebo (15.4 % vs 11.0 %).

From the short-term (6 weeks) schizophrenia trials there appears to be a dose-response relationship for akathisia in patients treated with asenapine, and for parkinsonism there was an increasing trend with higher doses.

Based on a small pharmacokinetic study, paediatric patients appeared to be more sensitive to dystonia with initial dosing with asenapine when a gradual up-titration schedule was not followed (see section 5.2). The incidence of dystonia in paediatric clinical trials using a gradual up-titration was similar to that seen in adult trials.

Weight increase
In the combined short-term and long-term schizophrenia and bipolar mania trials in adults, the mean change in body weight for asenapine was 0.8 kg. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at endpoint) in the short-term schizophrenia trials was 5.3 % for asenapine compared to 2.3 % for placebo. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at

endpoint) in the short-term, flexible-dose bipolar mania trials was 6.5 % for asenapine compared to 0.6 % for placebo.

In a 3-week, placebo-controlled, randomised, fixed-dose efficacy and safety trial in paediatric patients 10 to 17 years of age with bipolar I disorder, the mean change from baseline to endpoint in weight for placebo and asenapine 2.5 mg, 5 mg, and 10 mg twice daily, was 0.48, 1.72, 1.62, and 1.44 kg, respectively. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at Day 21) was 14.1 % for asenapine 2.5 mg twice daily, 8.9 % for asenapine 5 mg twice daily, and 9.2 % for asenapine 10 mg twice daily, compared to 1.1 % for placebo. In the long-term extension trial (50 weeks), a total of 34.8 % of subjects experienced clinically significant weight increase (i.e., ≥ 7 % increase in body weight at endpoint). Overall mean (SD) weight gain at study endpoint was 3.5 (5.76) kg.

Orthostatic hypotension
The incidence of orthostatic hypotension in elderly subjects was 4.1 % compared to 0.3 % in the combined phase 2/3 trial population.

Falls
Falls may occur as a result of one or more adverse events such as the following: Somnolence, Orthostatic hypotension, Dizziness, Extrapyramidal symptoms.

Hepatic enzymes
Transient, asymptomatic elevations of hepatic transaminases, alanine transferase (ALT), aspartate transferase (AST) have been seen commonly, especially in early treatment.

Other findings
Cerebrovascular events have been reported in patients treated with asenapine but there is no evidence of any excess incidence over what is expected in adults between 18 and 65 years of age.

Asenapine has anaesthetic properties. Oral hypoaesthesia and oral paraesthesia may occur directly after administration and usually resolves within 1 hour.

There have been post-marketing reports of serious hypersensitivity reactions in patients treated with asenapine, including anaphylactic/anaphylactoid reactions, angioedema, swollen tongue and swollen throat (pharyngeal oedema).

Paediatric population
Asenapine is not indicated for the treatment of children and adolescent patients below 18 years (see section 4.2).

The clinically relevant adverse experiences identified in the paediatric bipolar and schizophrenia trials were similar to those observed in adult bipolar and schizophrenia trials.

The most common adverse reactions (≥ 5 % and at least twice the rate of placebo) reported in paediatric patients with bipolar I disorder were somnolence, sedation, dizziness, dysgeusia, hypoaesthesia oral, paraesthesia oral, nausea, increased appetite, fatigue, and weight increased (see *Weight increase* above).

The most common adverse reactions (proportion of patients ≥ 5 % and at least twice placebo) reported in paediatric patients with schizophrenia were somnolence, sedation, akathisia, dizziness, and hypoaesthesia oral. There was a statistically significant higher incidence of patients with ≥ 7 % weight gain (from baseline to endpoint) compared to placebo (3.1 %) for Sycrest 2.5 mg twice daily (9.5 %) and Sycrest 5 mg twice daily (13.1 %).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Few cases of overdose were reported in the asenapine program. Reported estimated doses were between 15 and 400 mg. In most cases it was not clear if asenapine had been taken sublingually. Treatment-related adverse reactions included agitation and confusion, akathisia, orofacial dystonia, sedation, and asymptomatic ECG findings (bradycardia, supraventricular complexes, intraventricular conduction delay).

No specific information is available on the treatment of overdose with Sycrest. There is no specific antidote to Sycrest. The possibility of multiple medicinal product involvement should be considered. Cardiovascular monitoring is necessary to detect possible arrhythmias and management of overdose should concentrate on supportive therapy, maintaining an adequate airway oxygenation and ventilation, and management of symptoms. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulations may worsen hypotension in the setting of Sycrest-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medicinal products should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, antipsychotics, ATC code: N05AH05

Mechanism of action

The mechanism of action of asenapine 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.

Pharmacodynamic effects

Asenapine exhibits high affinity for serotonin 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT5, 5-HT6, and 5-HT7 receptors, dopamine D2, D3, D4, and D1 receptors, α1 and α2-adrenergic receptors, and histamine H1 receptors, and moderate affinity for H2 receptors. In *in vitro* assays asenapine acts as an antagonist at these receptors. Asenapine has no appreciable affinity for muscarinic cholinergic receptors.

Clinical efficacy

Clinical efficacy in bipolar I disorder

The efficacy of asenapine in the treatment of a DSM-IV manic or mixed episode of bipolar I disorder with or without psychotic features was evaluated in two similarly designed 3-week, randomised, double-blind, flexible-dose, placebo- and active controlled (olanzapine) monotherapy trials involving 488 and 489 patients, respectively. All patients met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnostic criteria for bipolar I disorder, current episode manic (DSM-IV 296.4x), or mixed (DSM-IV 296.6x) and had a Young Mania Rating Scale (Y-MRS) score of ≥ 20 at screening and baseline. Patients with rapid cycling were excluded from these studies. Asenapine demonstrated superior efficacy to placebo in the reduction of manic symptoms over 3 weeks. Point estimates [95 % CI] for the change from baseline to endpoint in YMRS using LOCF analysis in the two studies were as follows:
-11.5 [-13.0, -10.0] for asenapine vs -7.8 [-10.0, -5.6] for placebo and
-10.8 [-12.3, -9.3] for asenapine vs -5.5 [-7.5, -3.5] for placebo.
A statistically significant difference between asenapine and placebo was seen as early as day 2.

Patients from the two pivotal 3 week trials were studied for a further 9 weeks an extension trial. Maintenance of effect during the episode after 12 weeks of randomised treatment was demonstrated in this trial.

In one double-blind, fixed-dose, parallel-group, 3-week placebo controlled trial in subjects with bipolar I disorder experiencing an acute manic or mixed episode involving 367 patients of which 126 received placebo, 122 received asenapine 5 mg twice daily (BID), and 119 received asenapine 10 mg BID, the primary efficacy hypothesis was met. Both asenapine doses (5 mg BID and 10 mg BID) were superior to placebo and showed statistically significant improvement in change from baseline in Y-MRS total score at Day 21 compared with placebo. Based upon a LOCF analysis including all patients treated, the difference in least squares (LS) mean change from baseline to Day 21 in the Y-MRS total score between asenapine 5 mg BID and placebo was -3.1 points (95 % CI [-5.7, -0.5]; p-value = 0.0183). The difference in LS mean change from baseline to Day 21 in the Y-MRS total score between asenapine 10 mg BID and placebo was -3.0 points (95 % CI [-5.6, -0.4]; p-value = 0.0244). A statistically significant difference between asenapine and placebo was seen as early as day 2. In this short-term, fixed-dose controlled trial there was no evidence of added benefit with a 10 mg twice daily dose compared to 5 mg twice daily.

In a 12-week, placebo-controlled trial involving 326 patients with a manic or mixed episode of bipolar I disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of asenapine as adjunctive therapy resulted in superior efficacy to lithium or valproate monotherapy at week 3 (point estimates [95 % CI] for the change from baseline to endpoint in YMRS using LOCF analysis were -10.3 [-11.9, -8.8] for asenapine and -7.9 [-9.4, -6.4] for placebo) and at week 12 (-12.7 [-14.5, -10.9] for asenapine and -9.3 [-11.8, -7.6] for placebo) in the reduction of manic symptoms.

Paediatric population

Asenapine is not indicated for the treatment of children and adolescent patients below 18 years (see section 4.2).

The safety and efficacy of Sycrest was evaluated in 403 paediatric patients with bipolar I disorder who participated in a single, 3-week, placebo-controlled, double-blind trial, of whom 302 patients received Sycrest at fixed doses ranging from 2.5 mg to 10 mg twice daily. Study results showed statistically significant superiority for all three Sycrest doses in improving the Young Mania Rating Scale (YMRS) total score as measured by the change from baseline to Day 21, as compared with placebo. Long term efficacy could not be established in a 50-week, uncontrolled, open-label extension trial. The clinically relevant adverse reactions identified in the paediatric trials were generally similar to those observed in the adult trials. However, adverse effects of treatment on weight gain and on plasma lipid profile appeared to be greater than effects observed in the adult trials.

Efficacy of Sycrest was not demonstrated in an 8-week, placebo-controlled, double-blind, randomised, fixed-dose trial in 306 adolescent patients aged 12-17 years with schizophrenia at doses of 2.5 mg and 5 mg twice daily.

Paediatric studies with Sycrest were performed using flavoured sublingual tablets. The European Medicines Agency has deferred the obligation to submit the results of studies with Sycrest in one or more subsets of the paediatric population in bipolar I disorder (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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 (see section 4.2).

Distribution
Asenapine is rapidly distributed and has a large volume of distribution (approximately 20-25 L/kg), indicating extensive extravascular distribution. Asenapine is highly bound (95 %) to plasma proteins, including albumin and α1-acid glycoprotein.

Biotransformation
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. In an *in vivo* study in humans with radio-labelled asenapine, the predominant drug-related entity in plasma was asenapine N^+-glucuronide; others included N-desmethylasenapine, N-desmethylasenapine N-carbamoyl glucuronide, and unchanged asenapine in smaller amounts. Sycrest activity is primarily due to the parent compound.

Asenapine is a weak inhibitor of CYP2D6. Asenapine does not cause induction of CYP1A2 or CYP3A4 activities in cultured human hepatocytes. Co-administration of asenapine with known inhibitors, inducers or substrates of these metabolic pathways has been studied in a number of drug-drug interaction studies (see section 4.5).

Elimination
Asenapine is a high clearance compound, with a clearance after intravenous administration of 52 L/h. In a mass balance study, the majority of the radioactive dose was recovered in urine (about 50 %) and faeces (about 40 %), with only a small amount excreted in faeces (5-16 %) as unchanged compound. Following an initial more rapid distribution phase, the terminal half-life of asenapine is approximately 24 h.

Linearity/non-linearity
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.

During twice-daily dosing, steady-state is attained within 3 days. Overall, steady-state asenapine pharmacokinetics are similar to single-dose pharmacokinetics.

Pharmacokinetics in special populations

Hepatic impairment
The pharmacokinetics of asenapine were similar among subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment and subjects with normal hepatic function. In subjects with severe hepatic impairment (Child-Pugh C), a 7-fold increase in asenapine exposure was observed (see section 4.2).

Renal impairment
The pharmacokinetics of asenapine following a single dose of 5 mg asenapine were similar among subjects with varying degrees of renal impairment and subjects with normal renal function.

There is no experience with asenapine in severe renal impairment patients with a creatinine clearance less than 15 mL/min.

Elderly
In elderly patients (between 65 and 85 years of age), exposure to asenapine is approximately 30 % higher than in younger adults.

Paediatric population (children and adolescents)
In a PK study using unflavoured sublingual tablets, at the 5 mg twice daily dose level, asenapine pharmacokinetics in adolescent patients (12 to 17 years of age, inclusive) are similar to those observed in adults. In adolescents, the 10 mg twice daily dose did not result in increased exposure compared to 5 mg twice daily.

In a second PK study using flavoured sublingual tablets, the 10 mg twice daily dose in a paediatric population (10 to 17 years of age, inclusive) resulted in an approximate dose-proportional increase in asenapine exposure compared to 5 mg twice daily.

Gender
A population pharmacokinetic analysis indicated that there is no evidence of gender-related differences in the pharmacokinetics of asenapine.

Race

In a population pharmacokinetic analysis, no clinical relevant effects of race on the pharmacokinetics of asenapine were found.

Smoking status
A population pharmacokinetic analysis indicated that smoking, which induces CYP1A2, has no effect on the clearance of asenapine. In a dedicated study, concomitant smoking during administration of a single 5 mg sublingual dose had no effect on the pharmacokinetics of asenapine.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology. Repeat-dose toxicity studies in rat and dog showed mainly dose-limiting pharmacological effects, such as sedation. Furthermore, prolactin-mediated effects on mammary glands and oestrus cycle disturbances were observed. In dogs high oral doses resulted in hepatotoxicity that was not observed after chronic intravenous administration. Asenapine has some affinity to melanin-containing tissues. However, when tested *in vitro* it was devoid of phototoxicity. In addition, histopathological examination of the eyes from dogs treated chronically with asenapine did not reveal any signs of ocular toxicity, demonstrating the absence of a phototoxic hazard. Asenapine was not genotoxic in a battery of tests. In subcutaneous carcinogenicity studies in rats and mice, no increases in tumour incidences were observed. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Asenapine did not impair fertility in rats and was not teratogenic in rat and rabbit. Embryotoxicity was found in reproduction toxicology studies using rats and rabbits. Asenapine caused mild maternal toxicity and slight retardation of foetal skeletal development. Following oral administration to pregnant rabbits during the period of organogenesis, asenapine adversely affected body weight at the high dose of 15 $mg.kg^{-1}$ twice daily. At this dose foetal body weight decreased. When asenapine was administered intravenously to pregnant rabbits, no signs of embryotoxicity were observed. In rats, embryofoetal toxicity (increased post-implantation loss, decreased foetal weights, and delayed ossification) was observed following oral or intravenous administration during organogenesis or throughout gestation. Increased neonatal mortality was observed among the offspring of female rats treated during gestation and lactation. From a cross-fostering study it was concluded that asenapine induced peri- and postnatal losses are caused by impairment of the pups rather than altered nursing behaviour of the dams.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Mannitol (E421)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Peelable aluminium/aluminium blisters in cartons of 20, 60 or 100 sublingual tablets per carton.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Organon Pharma (UK) Limited
Shotton Lane
Cramlington
NE23 3JU
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00025/0659

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

13/11/2024