ANNEX I

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 a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet
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

Manic episode
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.

Additional information on special populations

Paediatric population
The safety and efficacy of Sycrest in children aged below 18 years have not been established. Limited safety data with Sycrest are available in adolescent patients. A pharmacokinetic study was performed in adolescent patients. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Elderly patients
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.

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

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 medication, 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.

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 medicines. 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 antipsychotic medicinal products, including 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.

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 medicines 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 BID 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 medicines
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.

To ensure optimal absorption, eating and drinking should be avoided for 10 minutes after administration.

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).

Neonates 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 neonates. Consequently, newborns should be monitored carefully.

Sycrest should not be used during pregnancy unless clearly necessary 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. It is recommended that women receiving Sycrest should not breast-feed.

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

No studies on the effects on the ability to drive and use machines have been performed. Asenapine may cause somnolence and sedation. Therefore, patients should be cautioned about operating machinery, including motor vehicles, until they are reasonably certain that Sycrest therapy does not affect them adversely.

4.8 Undesirable effects

The most frequently reported adverse drug reactions during treatment with asenapine were somnolence and anxiety. The incidences of the Adverse Drug Reactions (ADRs) associated with asenapine therapy are tabulated below. The table is based on adverse events 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), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events are qualified as "not known".

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	Neuroleptic malignant syndrome	
Eye disorders				Accommodation disorder	
Cardiac disorders			Sinus bradycardia Bundle branch block		

			Electrocardio-gram QT prolonged		
Vascular disorders			Orthostatic hypotension Hypotension		
Respiratory, thoracic and mediastinal disorders				Pulmonary embolism	
Gastrointestinal disorders		Hypoaesthesia oral	Swollen tongue Dysphagia Glossodynia Paraesthesia oral		
Hepatobiliary disorders		Alanine aminotransferase increased			
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			

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.

Weight increase
In the combined short-term and long-term schizophrenia and bipolar mania trials, 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 bipolar mania trials was 6.5 % for asenapine compared to 0.6 % for placebo.

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.

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 postmarketing reports of serious hypersensitivity reactions in patients treated with asenapine, including swollen tongue and swollen throat (pharyngeal oedema).

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 medicines 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, 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.

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, randomized, double-blind, 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 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-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
The European Medicines Agency has deferred the obligation to submit the results of studies with asenapine 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 1700 l), indicating extensive extravascular distribution. Asenapine is highly bound (95 %) to plasma proteins, including albumin and α1-acid glycoprotein.

Biotransformation
Asenapine is extensively metabolized. 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

Hepatically impaired patients
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).

Renally impaired patients
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 (Adolescents)
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.

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

7. MARKETING AUTHORISATION HOLDER

N.V. Organon, Kloosterstraat 6, NL-5349 AB Oss, The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/640/001
EU/1/10/640/002
EU/1/10/640/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 September 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 10 mg sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 10 mg asenapine (as maleate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet
Round, white to off-white, sublingual tablets debossed with ”10” 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

Manic episode
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.

Additional information on special populations

Paediatric population
The safety and efficacy of Sycrest in children aged below 18 years have not been established. Limited safety data with Sycrest are available in adolescent patients. A pharmacokinetic study was performed in adolescent patients. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Elderly patients
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.

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

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 medication, 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.

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 medicines. 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 antipsychotic medicinal products, including 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.

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 medicines 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 BID 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 medicines
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.

To ensure optimal absorption, eating and drinking should be avoided for 10 minutes after administration.

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).

Neonates 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 neonates. Consequently, newborns should be monitored carefully.

Sycrest should not be used during pregnancy unless clearly necessary 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. It is recommended that women receiving Sycrest should not breast-feed.

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

No studies on the effects on the ability to drive and use machines have been performed. Asenapine may cause somnolence and sedation. Therefore, patients should be cautioned about operating machinery, including motor vehicles, until they are reasonably certain that Sycrest therapy does not affect them adversely.

4.8 Undesirable effects

The most frequently reported adverse drug reactions during treatment with asenapine were somnolence and anxiety. The incidences of the Adverse Drug Reactions (ADRs) associated with asenapine therapy are tabulated below. The table is based on adverse events 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), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events are qualified as "not known".

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	Neuroleptic malignant syndrome	
Eye disorders				Accommodation disorder	
Cardiac disorders			Sinus bradycardia Bundle branch block		

			Electrocardiogram QT prolonged		
Vascular disorders			Orthostatic hypotension Hypotension		
Respiratory, thoracic and mediastinal disorders				Pulmonary embolism	
Gastrointestinal disorders		Hypoaesthesia oral	Swollen tongue Dysphagia Glossodynia Paraesthesia oral		
Hepatobiliary disorders		Alanine aminotransferase increased			
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			

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.

Weight increase
In the combined short-term and long-term schizophrenia and bipolar mania trials, 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 bipolar mania trials was 6.5 % for asenapine compared to 0.6 % for placebo.

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.

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 postmarketing reports of serious hypersensitivity reactions in patients treated with asenapine, including swollen tongue and swollen throat (pharyngeal oedema).

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 medicines 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, 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.

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, randomized, double-blind, 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 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-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
The European Medicines Agency has deferred the obligation to submit the results of studies with asenapine 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 1700 l), indicating extensive extravascular distribution. Asenapine is highly bound (95 %) to plasma proteins, including albumin and α1-acid glycoprotein.

Biotransformation
Asenapine is extensively metabolized. 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

Hepatically impaired patients
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).

Renally impaired patients
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 (Adolescents)
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.

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

7. MARKETING AUTHORISATION HOLDER

N.V. Organon, Kloosterstraat 6, NL-5349 AB Oss, The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/640/004
EU/1/10/640/005
EU/1/10/640/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 September 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Organon (Ireland) Ltd.
Drynam Road, Swords, Co. Dublin
Ireland

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version INT00137451 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (5 mg)

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 5 mg sublingual tablets
asenapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 sublingual tablets
60 sublingual tablets
100 sublingual tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Sublingual use
Peelable blister. Do not crush, chew or swallow.
Keep the tablet under your tongue until it dissolves.
Do not eat or drink for 10 minutes after taking the tablet.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
NL- 5349 AB Oss
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/640/001 20 sublingual tablets
EU/1/10/640/002 60 sublingual tablets
EU/1/10/640/003 100 sublingual tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

sycrest 5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (5 mg)

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 5 mg sublingual tablets
asenapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (10 mg)

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 10 mg sublingual tablets
asenapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 10 mg asenapine (as maleate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 sublingual tablets
60 sublingual tablets
100 sublingual tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Sublingual use
Peelable blister. Do not crush, chew or swallow.
Keep the tablet under your tongue until it dissolves.
Do not eat or drink for 10 minutes after taking the tablet.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
NL- 5349 AB Oss
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/640/004 20 sublingual tablets
EU/1/10/640/005 60 sublingual tablets
EU/1/10/640/006 100 sublingual tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

sycrest 10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (10 mg)

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 10 mg sublingual tablets
asenapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Sycrest 5 mg sublingual tablets
Sycrest 10 mg sublingual tablets
asenapine

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT SYCREST IS AND WHAT IT IS USED FOR

Sycrest belongs to a group of medicines called antipsychotics and is used to treat moderate to severe manic episodes associated with bipolar I disorder. Antipsychotic medicines affect the chemicals that allow communication between nerve cells (neurotransmitters). Illnesses that affect the brain, such as bipolar I disorder, may be due to certain chemicals in the brain, such as dopamine and serotonin, being out of balance and these imbalances may cause some of the symptoms you may be experiencing. Exactly how Sycrest works is unknown, however, it is believed to adjust the balance of these chemicals.
Manic episodes associated with bipolar I disorder is a condition with symptoms such as feeling “high”, having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability.

2. BEFORE YOU TAKE SYCREST

Do not take Sycrest
If you are allergic (hypersensitive) to asenapine or any of the other ingredients (listed in section 6 Further information).

Take special care with Sycrest
Sycrest has not been studied in elderly patients with dementia. However, elderly patients with dementia, who are treated with other similar types of medicine, may have an increased risk of stroke or death. Sycrest is not approved for the treatment of elderly patients with dementia and is not recommended for use in this particular group of patients.

Sycrest may cause low blood pressure. In the early stages of treatment, some people may faint, especially when getting up from a lying or sitting position. This will usually pass on its own but if it does not, tell your doctor. Your dose may need to be adjusted.

Sycrest may cause weight gain.

Tell your doctor immediately if you experience

- involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of Sycrest may be needed.
- fever, severe muscle stiffness, sweating or a lowered level of consciousness (a disorder called "neuroleptic malignant syndrome"). Immediate medical treatment may be needed.

Check with your doctor or pharmacist before taking Sycrest:

- if you have ever been diagnosed with a condition whose symptoms include high body temperature and muscle stiffness (also known as neuroleptic malignant syndrome).
- if you have ever experienced abnormal movements of the tongue or face (tardive dyskinesia). You should be aware that both of these conditions may be caused by this type of medicine.
- if you have a heart disease or a treatment for heart disease that makes you prone to low blood pressure
- if you are diabetic or prone to diabetes
- you have Parkinson's disease or dementia
- if you have epilepsy (seizures)
- if you experience any difficulty in swallowing (dysphagia)
- if you have severe liver problems. If you do, you should not take Sycrest
- if you have difficulty controlling core body temperature
- if you have thoughts of suicide

Be sure to tell your doctor if you meet any of these conditions as he/she may want to adjust your dose or monitor you for a while. Also contact your doctor immediately if any of these conditions develops or worsens while using Sycrest.

Children and adolescents
Use of Sycrest below the age of 18 years is not recommended due to lack of information on whether it is safe and effective in this age group.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Some medicines may reduce the effect of Sycrest.

If you are taking other medicines, Sycrest should be taken last.

You should tell your doctor if you are taking antidepressant medicines (specifically fluvoxamine, paroxetine or fluoxetine), as it may be necessary to change your Sycrest or antidepressant medicine dose.

You should tell your doctor if you are taking medicines for Parkinson's disease (such as levodopa), as Sycrest may make them less effective.

Since Sycrest works primarily in the brain, interference from other medicines (or alcohol) that work in the brain could occur due to an additive effect on brain function.

Since Sycrest can lower blood pressure, care should be taken when Sycrest is taken with other medicines that lower blood pressure.

Taking Sycrest with food and drink
Do not eat or drink for 10 minutes after taking the tablet.
You should avoid drinking alcohol when taking Sycrest.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Do not take Sycrest while you are pregnant, unless your doctor tells you so. If you are taking Sycrest and you become pregnant or you plan to get pregnant, ask your doctor as soon as possible whether you may continue taking Sycrest.

Do not breast-feed when taking Sycrest.

The following symptoms may occur in newborn babies, of mothers that have used Sycrest in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

Driving and using machines
Sycrest may affect your concentration or alertness. Make sure these abilities are not affected before you drive or operate machinery.

3. HOW TO TAKE SYCREST

Always take Sycrest exactly as your doctor or pharmacist has told you. Sycrest is not advised if you are unable to take the tablet as described below.You should check with your doctor or pharmacist if you are not sure. If you are unable to take Sycrest as is described below, the treatment may not be effective for you.
The usual dose is a tablet of 5 mg or 10 mg two times a day. One dose should be taken in the morning and one dose should be taken in the evening.

Instructions for use
- Do not remove a tablet from the blister until ready to take it.
- Use dry hands when touching the tablet.
- Do not push the tablet through the blister. Do not cut or tear the blister.
- Peel back the coloured tab (Figure 1).
- Gently remove the tablet (Figure 2). Do not crush the tablet.
- To ensure optimal absorption, place the tablet under the tongue and wait until it dissolves completely (Figure 3). The tablet will dissolve in saliva within seconds.
- Do not swallow or chew on the tablet.
- Do not eat or drink for 10 minutes after taking the tablet.

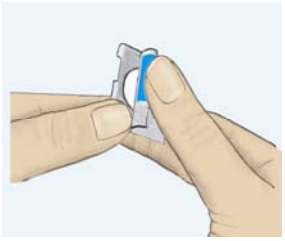
Figure 1

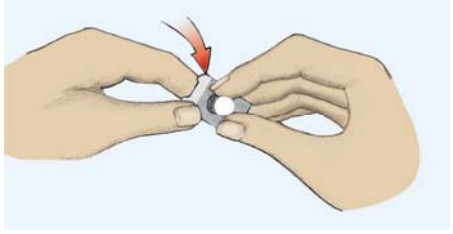
Figure 2


Figure 3

If you take more Sycrest than you should
If you take too much Sycrest, contact a doctor straight away. Take the medicine pack with you. In case of overdose you may feel sleepy or tired, or have abnormal body movements, problems with standing and walking, feel dizzy due to low blood pressure and feel agitated and confused.

If you forget to take Sycrest
Do not take a double dose to make up for a forgotten dose. If you miss one dose, take your next dose as usual. If you miss two or more doses, contact your doctor.

If you stop taking Sycrest
If you stop taking Sycrest, you will lose the effects of this medicine. You should not stop taking this medicine, unless your doctor tells you as your symptoms may return.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Sycrest can cause side effects, although not everybody gets them.

Very common side effects (affects more than 1 user in 10)
- anxiety
- sleepiness

Common side effects (affects 1 to 10 users in 100)
- weight gain
- increased appetite
- slow or sustained muscle contractions
- restlessness
- involuntary muscle contractions
- slow movements, tremor
- sedation
- dizziness
- change in taste
- numb feeling of the tongue or in the mouth
- muscle tightness
- fatigue
- increase in the level of liver proteins

Uncommon side effects (affects 1 to 10 users in 1,000)
- high blood sugar
- fainting episode
- convulsion
- abnormal muscle movements: a collection of symptoms known as extrapyramidal symptoms (EPS) which may include one or more of the following: abnormal movements of muscles, tongue, or jaw, slow or sustained muscle contractions, muscle spasms, tremor (shaking), abnormal movements of the eyes, involuntary muscle contractions, slow movements, or restlessness
- speech problems
- abnormal slow heartbeat
- middle heart block
- abnormal electrocardiogram (prolongation of the QT interval)
- low blood pressure upon standing
- low blood pressure
- tingling of the tongue or in the mouth
- swollen or painful tongue
- difficulty in swallowing
- sexual dysfunction
- lack of regular menstrual periods

Rare side effects (affects 1 to 10 users in 10,000)
- changes in the levels of white blood cells
- neuroleptic malignant syndrome (confusion, reduced or loss of consciousness, high fever, and severe muscle stiffness)
- difficulties in focusing with the eyes
- blood clots in blood vessels to the lungs causing chest pain and difficulty in breathing
- muscle disease presenting as unexplained aches and pains
- male breast enlargement
- leakage of milk or fluid from the breast

Side effects with unknown frequency
- allergic reactions (these usually involve a combination of effects such as difficulty in breathing, swollen tongue or throat, skin rash, itching and increased heart rate. Seek medical attention immediately if you experience these symptoms).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE SYCREST

Keep out of the reach and sight of children.

Do not use Sycrest after the expiry date which is stated on the blister and on the carton. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture.

This medicinal product does not require any special temperature storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Sycrest contains
– The active substance is asenapine. Each Sycrest tablet contains either 5 mg or 10 mg of the active substance. The exact amount is shown on your Sycrest tablet pack.
– The other ingredients are gelatin and mannitol (E421).

What Sycrest looks like and contents of the pack
The 5 mg sublingual tablets are round white to off-white tablets marked with “5” on one side.
The 10 mg sublingual tablets are round white to off-white tablets marked with “10” on one side.

The sublingual tablets are provided in peelable blisters containing 10 tablets each. Packs may contain 20, 60 or 100 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
N.V. Organon
Kloosterstraat 6
NL-5349 AB Oss
The Netherlands

Manufacturer
Organon (Ireland) Ltd.
Drynam Road, Swords
Co. Dublin, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Lundbeck S.A.
Avenue Molière 225/Molierelaan 225

Luxembourg/Luxemburg
Lundbeck S.A.
Avenue Molière 225/Molierelaan 225

B-1050 Bruxelles/Brussel
Tél/Tel: +32 2 340 2828

България
Lundbeck Export A/S Representative Office
EXPO 2000
Vaptzarov Blvd. 55
Sofia 1407
Тел.: +359 2962 4696

Česká republika
Lundbeck Česká republika s.r.o.
Bozděchova 7
CZ-150 00 Praha 5
Tel: +420 225 275 600

Danmark
Lundbeck Pharma A/S
Dalbergstrøget 5
DL-2630 Taastrup
Tel: + 45 4371 4270

Deutschland
Lundbeck GmbH
Karnapp 25
D-21079 Hamburg
Tel: +49 40 23649 0

Eesti
Lundbeck Eesti A/S
Weizenbergi 29
EE-10150 Tallinn
Tel: + 372 605 9350

Ελλάδα
Lundbeck Hellas S.A.
64, Kifisias Avenue
GR-151 25 Marousi, Athens
Τηλ: + 30 210 610 5036

España
Lundbeck España S.A.
Av. Diagonal, 605, 9°-1ª
E-08028 Barcelona
Tel: +34 93 494 9620

France
Lundbeck SAS
37-45, quai du Président Roosevelt
F-92445 Issy-les-Moulineaux Cedex
Tél: + 33 1 79 41 29 00

Ireland
Lundbeck (Ireland) Ltd

B-1050 Bruxelles/Brussel
Tél/Tel: +32 2 340 2828

Magyarország
Lundbeck Hungária Kft.
Montevideo utca 3/b
H-1037 Budapest
Tel.: +36 1 436 9980

Malta
Charles di Girogio Ltd
Triq il-Kanonku Kamenu Pirrota
MT-1114 B'Kara BKR
Tel: +356 25600500

Nederland
Lundbeck B.V.
Plaza Arena, Jupiter Gebouw
Herikerbergweg 100
NL-1101 CM Amsterdam
Tel: +31 20 697 1901

Norge
H. Lundbeck AS
Strandveien 15 B
N-1366 Lysaker
Tlf: + 47 91 300 800

Österreich
Lundbeck Austria GmbH
Dresdner Strasse 82
A-1200 Vienna
Tel: + 43 1 331 070

Polska
Lundbeck Poland Sp. z o. o.
ul. Krzywickiego 34
PL-02-078 Warszawa
Tel.: + 48 22 626 9300

Portugal
Lundbeck Portugal Lda
Quinta da Fonte
Edifício D. João I – Piso 0 Ala A
P-2770-203 Paço d'Arcos
Tel: +351 21 00 45 900

România
Lundbeck România
Str. Ghiocei no.7A, Sector 2
RO-020571 Bucureşti
Tel: +40 21319 88 26

Slovenija
Lundbeck Pharma d.o.o.

7 Riverwalk
Citywest Business Campus
IRL - Dublin 24
Tel: +353 1 468 9800

Ísland
Lundbeck Export útibú á Íslandi
Ármúla 1
IS-270 Reykjavík
Sími: + 354 414 7070

Italia
Lundbeck Italia S.p.A.
Via G. Fara 35
I-20124 Milan
Tel: +39 02 677 4171

Κύπρος
Lundbeck Hellas A.E
Θεμ. Δέρβη-Φλωρίνης
STADYL BUILDING
CY-1066 Λευκωσία
Τηλ.: + 357 22490305

Latvija
SIA Lundbeck Latvia
Kleistu iela 24
Rīga, LV 1067
Tel: + 371 6 7 067 884

Lietuva
UAB Lundbeck Lietuva
L. Stuokos-Gucevičiaus 9-3
LT 01122 Vilnius
Tel: + 370 5 231 4188

Titova cesta 8
SI-2000 Maribor
Tel.: +386 2 229 4500

Slovenská republika
Lundbeck Slovensko s.r.o.
Zvolenská 19
SK-821 09 Bratislava 2
Tel: +421 2 5341 4218

Suomi/Finland
Oy H. Lundbeck Ab
Itäinen Pitkäkatu 4 / Österlånggatan 4
FIN-20520 Turku/Åbo
Puh/Tel: + 358 2 276 5000

Sverige
H. Lundbeck AB
Box 23
S-250 53 Helsingborg
Tel: + 46 42 25 43 00

United Kingdom
Lundbeck Limited
Lundbeck House
Caldecotte Lake Business Park
Caldecotte
Milton Keynes MK7 8LG - UK
Tel: +44 1908 649 966

This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.