AUSTRALIAN PRODUCT INFORMATION

SAPHRIS®

asenapine (as maleate)

1 NAME OF THE MEDICINE

Asenapine (as maleate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SAPHRIS is available as 5 mg and 10 mg wafers containing 5 mg asenapine (7.03 mg asenapine maleate) and 10 mg asenapine (14.06 mg asenapine maleate), respectively.

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

SAPHRIS 5 mg contains 5 mg of asenapine as maleate. It is a round wafer, white to off-white in colour with “5” debossed on one side.

SAPHRIS 10 mg contains 10 mg of asenapine as maleate. It is a round wafer, white to off-white in colour with “10” debossed on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SAPHRIS is indicated in the:

- treatment of schizophrenia in adults
- treatment of acute manic or mixed episodes associated with Bipolar 1 Disorder in adults as monotherapy or in combination with lithium or sodium valproate
- prevention of relapse of manic or mixed episodes in Bipolar 1 Disorder in adults as monotherapy or in combination with lithium or sodium valproate

4.2 DOSE AND METHOD OF ADMINISTRATION

Schizophrenia
The recommended dose range of SAPHRIS is 5 mg to 10 mg twice daily. SAPHRIS should be administered at an initial daily dose of 5 mg twice daily. An increase in dose to 10 mg twice daily is recommended only after clinical assessment. In controlled trials, there was no suggestion of added benefit with a higher dose of 10 mg twice daily but there was a clear increase in certain adverse reactions. The safety of doses above 10 mg twice daily has not been evaluated in clinical trials (see **Section 5.1 Pharmacodynamic Properties, Clinical trials**).

Acute and maintenance treatment of manic or mixed episodes in Bipolar 1 Disorder
The recommended starting dose of SAPHRIS as monotherapy is 10 mg twice daily. 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. SAPHRIS has not been adequately assessed for the long term treatment of patients with Bipolar 1 Disorder. It has shown efficacy in the prevention of relapse of manic or mixed episodes when used as monotherapy or in combination with lithium or sodium valproate

for up to 12 weeks. When used as monotherapy or in combination with lithium or sodium valproate, it is generally recommended that responding patients be continued beyond the acute response. If SAPHRIS is used for extended periods in Bipolar 1 Disorder, the long-term risks and benefits of the drug for the individual patient should be periodically re-evaluated.

Method of administration:
The wafer should not be removed from the blister until ready to take it. Use dry hands when handling the wafer. Do not push the wafer through the wafer pack. Do not cut or tear the wafer pack. Peel back the coloured tab and gently remove the wafer. Do not crush the wafer.

To ensure optimal absorption, place the SAPHRIS wafer under the tongue and allow it to dissolve completely. The wafer will dissolve in saliva within seconds. Do not chew or swallow the SAPHRIS wafers. Do not eat or drink for 10 minutes.

When used in combination with other medication, SAPHRIS should be taken last.

Treatment with SAPHRIS 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).

Elderly
SAPHRIS should be used with care in the elderly. Limited data on safety and efficacy are available in patients 65 years of age or older (see **Section 5.2 Pharmacokinetic Properties, Special populations**).

Renal impairment
No dosage adjustment is required for patients with renal impairment.

Hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment. In subjects with severe hepatic impairment (Child-Pugh C), a 7-fold increase in asenapine exposure was observed. Thus, SAPHRIS is not recommended in patients with severe hepatic impairment (see **Section 5.2 Pharmacokinetic Properties, Special populations**).

Children
Use of SAPHRIS in children below the age of 18 is not recommended.

4.3 CONTRAINDICATIONS

SAPHRIS is contraindicated in:

- Patients who are hypersensitive to any component of the wafer or to asenapine. Hypersensitivity reactions, including anaphylaxis and angioedema, have been observed in patients treated with asenapine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Elderly patients with dementia-related psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. A meta-analysis of 17 placebo controlled trials with dementia related behavioural disorders showed a risk of death in the drug treated patients of approximately 1.6 to 1.7 times that seen in placebo treated patients. The clinical trials included in the meta-analysis were undertaken with Zyprexa (olanzapine), Abilify (aripiprazole), Risperdal (risperidone) and Seroquel (quetiapine). Over the course of these trials averaging about ten weeks in duration, the rate of death in drug treated patients was about 4.5% compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure,

sudden death) or infectious (e.g. pneumonia) in nature. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis.

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 SAPHRIS. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure.

If a patient develops signs and symptoms indicative of NMS, SAPHRIS must be discontinued.

Seizures

In clinical trials, cases of seizure were occasionally reported during treatment with SAPHRIS. Therefore, SAPHRIS 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 schizophrenia and bipolar disorder; close supervision of high-risk patients should accompany treatment. Prescriptions for SAPHRIS should be written for the smallest quantity of wafers, consistent with good patient management, in order to reduce the risk of overdose.

Weight increase

In the combined short-term and long-term schizophrenia and bipolar mania trials, the mean weight change for patients treated with asenapine was 0.8 kg. The mean body weight change from baseline to endpoint in the placebo-controlled short-term schizophrenia trials was 1.1 kg for SAPHRIS, 0.1 kg for placebo, and 2.4 kg for olanzapine. The proportion of subjects with clinically significant weight gain (>7% weight gain from baseline to endpoint) in the short-term schizophrenia trials was 5.3% for asenapine-treated subjects compared to 2.3% for placebo. In the placebo-controlled short-term bipolar mania trials, mean weight changes were 1.3 kg for SAPHRIS, 0.2 kg for placebo, and 2.3 kg for olanzapine. The proportion of subjects with clinically significant weight gain in the short-term bipolar mania trials was 6.5% for asenapine-treated patients compared with 0.6% for placebo.

In the open-label phase of Study A7501012 the mean change in body weight from baseline to open-label endpoint was 0.5 kg. Clinically relevant weight gain (> 7% from baseline) occurred in 7.0% of the subjects, while clinically relevant weight loss occurred in 4.3%. In the double-blind phase, mean change in body weight from double-blind baseline to double-blind endpoint was -1.2 kg in the placebo treatment group and 0.0 kg in the asenapine treatment group. Clinically relevant weight gain in the double-blind phase occurred in 3.7% of the asenapine-treated subjects and in 0.5% of the placebo-treated subjects, while clinically relevant weight loss occurred in 3.2% of the asenapine subjects and in 9.6% of placebo subjects. There were no subjects in either the asenapine or placebo group who discontinued from the study due to weight increased or weight decreased.

In the long-term trials, the mean body weight changes from baseline to endpoint for SAPHRIS were 0.6 kg and 2.0 kg (schizophrenia and bipolar mania trials, respectively). The mean body weight changes in these trials for olanzapine were 3.7 kg and 4.5 kg (schizophrenia and bipolar mania trials, respectively).

Orthostatic hypotension

SAPHRIS 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. In clinical trials, cases of syncope were

occasionally reported during treatment with SAPHRIS. As with other atypical antipsychotics, SAPHRIS should be used with caution in elderly patients and patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolaemia, and treatment with antihypertensive medications).

Tardive dyskinesia

Medicines 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 SAPHRIS. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on SAPHRIS, discontinuation of treatment should be considered.

SAPHRIS should be prescribed in a manner that is most likely to minimise the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

Hyperprolactinaemia

Like other drugs that antagonise dopamine D_2 receptors, SAPHRIS can elevate prolactin levels, and the elevation can persist during chronic administration. Hyperprolactinaemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhoea, amenorrhoea and gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinaemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. In SAPHRIS clinical trials, the incidence of adverse events related to abnormal prolactin levels were 0.4% versus 0% for placebo.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously-detected breast cancer. Neither clinical studies nor epidemiological studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Leukopenia, neutropenia, and agranulocytosis

In clinical trials and postmarketing experience, events of leukopenia/neutropenia have been reported temporarily related to antipsychotic agents, including SAPHRIS. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (BC) monitored frequently during the first few months of therapy and SAPHRIS should be discontinued at the first signs of decline in WBC in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe

neutropenia (absolute neutrophil count < 1000/mm^3) should discontinue SAPHRIS and have their WBC followed until recovery.

QT interval

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

The effects of asenapine on the QT/QTc interval were evaluated in a dedicated QT study. This trial involved asenapine doses of 5 mg, 10 mg, 15 mg and 20 mg twice daily and placebo, and was conducted in 151 clinically stable patients with schizophrenia with electrocardiographic assessments throughout the dosing interval at baseline and steady state. At these doses, asenapine was associated with increases in QTc interval ranging from 2 to 5 msec compared to placebo. No patients treated with SAPHRIS experienced QTc increases ≥ 60 msec from baseline measurement, nor did any patient experience a QTc of ≥ 500 msec.

Electrocardiogram (ECG) measurements were taken at various time points during the SAPHRIS clinical trial program (5 mg or 10 mg twice daily doses). Post-baseline QT prolongations exceeding 500 msec were reported at comparable rates for asenapine and placebo in these short-term trials.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia has been reported in patients treated with atypical antipsychotics including SAPHRIS. In clinical trials with SAPHRIS, there were no significant differences in the incidence rates of hyperglycaemia-related adverse events compared to placebo. However, in short term clinical studies there was a mean increase in fasting insulin of 11.8 pmol/L for subjects given asenapine. The increase in fasting insulin was less than occurred in subjects given olanzapine (23.8 pmol/L). 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 and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycaemic-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Metabolic changes

SAPHRIS is associated with metabolic changes in adults and children. These metabolic changes are weight increased (including severe weight gain of > 7% of total body weight), hyperglycaemia and Diabetes Mellitus and dyslipidaemia. The frequency and severity of these risks appear higher in children compared to adults. Cases of Metabolic Syndrome, as defined

by the International Diabetes Federation, have been observed in paediatric subjects exposed to SAPHRIS in short-term clinical studies.

In adult trials, incidence of weight gain > 7% varied, with rates ranging from 6-7%. Hyperglycaemia and Diabetes Mellitis have been observed in patients treated with asenapine. According to the Australian Psychotropic Therapeutic Guidelines (2013), dyslipidaemia is listed as occurring moderately frequently in adults.

Paediatric subjects
SAPHRIS is not approved for use in subjects <18 years of age.

In a 3-week paediatric trial of 403 subjects with bipolar 1 disorder (Study P06107), weight gain of > 7 % was seen in 8.9%-14.1% of patients. There was evidence of abnormalities of blood insulin and blood sugar and clear evidence of dyslipidaemia. Eleven subjects (2.8%) developed new-onset Metabolic Syndrome, compared to no subjects in placebo. In the long-term, open-label extension trial (50 weeks), 34.8% of subjects experienced weight increase of ≥ 7% of total body weight.

In an 8-week study of 306 patients with schizophrenia (Study P05896), severe weight gain was significantly higher in 5 mg BID group compared to placebo, occurring at a frequency of 13%. A pattern for increase in both insulin and fasting insulin was observed in the asenapine treatment groups in a dose-dependent fashion. Lipids parameters were generally higher in the treatment groups compared to placebo. Three subjects (1%) developed new-onset Metabolic Syndrome in the SAPHRIS treatment groups, compared to no subjects in placebo.

Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic treatment. Cases of dysphagia were occasionally reported in patients treated with SAPHRIS.

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 SAPHRIS 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.

Extrapyramidal symptoms (EPS)

From the short-term (6 week) 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.

The presentation of akathisia may be variable and comprise subjective complaints of restlessness and an overwhelming urge to move presenting as either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot or both. Particular attention should be paid to the monitoring for such symptoms and signs as left untreated akathisia is associated with poor compliance and increased risk of relapse.

In the long term trials the overall incidence of EPS for subjects treated with SAPHRIS 5-10 mg twice daily was approximately 16% for both the schizophrenia population (olanzapine 7.7%); and the bipolar mania population (olanzapine 16.2%).

Parkinson's disease

Physicians should weigh the risks versus the benefits when prescribing asenapine 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. Manifestations 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.

Use in hepatic impairment

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

Use in renal impairment

See **Section 4.2 Dose and Method of Administration, Renal impairment**.

Use in the elderly

See **Section 4.2 Dose and Method of Administration, Elderly**.

Paediatric use

SAPHRIS is not recommended for use in children and adolescents below 18 years of age.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Given the primary CNS effects of asenapine (see **Section 4.8 Adverse Effects (Undesirable Effects)**), caution should be used when it is taken in combination with other centrally acting drugs. Patients should be advised to avoid alcohol while taking SAPHRIS.

Potential for other medicines to affect SAPHRIS

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 (Table 1). With the exception of fluvoxamine (strong CYP1A2 inhibitor), none of the interacting drugs resulted in clinically relevant alterations in asenapine pharmacokinetics.

Table 1
The potential effects of inhibitors and an inducer of CYP enzyme pathways on asenapine pharmacokinetics

Coadministered drug (Postulated effect on CYP450/UGT)	Dose schedules		Effect on asenapine pharmacokinetics		**Recommendation**
	Coadministered drug	Asenapine	C_{max}	$AUC_{0-\infty}$	

Fluvoxamine (CYP1A2 inhibitor)	25 mg twice daily for 8 days	5 mg Single Dose	+13%	+29%	Coadminister with caution*
Paroxetine (CYP2D6 inhibitor)	20 mg once daily for 9 days	5 mg Single Dose	–13%	–9%	No SAPHRIS dose adjustment required *[see potential for SAPHRIS to affect other medicines]*
Imipramine (CYP1A2/2C19/3A4 inhibitor)	75 mg Single Dose	5 mg Single Dose	+17%	+10%	No SAPHRIS dose adjustment required
Cimetidine (CYP3A4/2D6/1A2 inhibitor)	800 mg twice daily for 8 days	5 mg Single Dose	–13%	+1%	No SAPHRIS dose adjustment required
Carbamazepine (CYP3A4 inducer)	200mg twice daily for 4 days 400 mg twice daily for 15 days	5 mg Single Dose	–16%	–16%	No SAPHRIS dose adjustment required
Valproate (UGT1A4 inhibitor)	500 mg twice daily for 9 days	5 mg Single Dose	2%	–1%	No SAPHRIS adjustment required

*The full therapeutic dose of fluvoxamine would be expected to cause a greater increase in asenapine plasma concentrations

Potential for SAPHRIS to affect other medicines

Because of its α1-adrenergic antagonism with potential for inducing orthostatic hypotension (see **Section 4.4 Special Warnings and Precautions for Use**), SAPHRIS may enhance the effects of certain antihypertensive agents.

In vitro studies indicate that asenapine weakly inhibits CYP2D6. Following coadministration 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, coadministration 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). Coadministration 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, SAPHRIS should be coadministered cautiously with drugs that are both substrates and inhibitors for CYP2D6.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility in rats was unaffected by oral asenapine administration that resulted in an estimated drug exposure (based on plasma AUC) 11 fold that expected in humans with the maximum recommended dose.

Use in pregnancy (Category C)

There are no adequate data from the use of SAPHRIS in pregnant women. Asenapine was not teratogenic in rats or rabbits at oral or intravenous doses that resulted in estimated drug exposures up to 11 (rat, based on plasma AUC) or 24 (rabbit, based on body surface area)

times the expected human values with the maximum recommended dose. Reproductive toxicity studies were conducted using oral and intravenous routes, rather than the sublingual route used clinically. Increases in pre- and post-implantation losses were observed in some studies in rats, with pre-implantation loss increased after oral doses that resulted in estimated exposures (based on AUC) 3 times that expected in humans at the maximum recommended dose.

In rats treated intravenously from early gestation to weaning, increased early mortality and reduced weight gain were seen in pups at maternal doses resulting in exposures (based on AUC) approximately 3 fold that expected in humans at the maximum recommended dose. A cross-fostering study suggests that the increased pup mortality was mainly due to prenatal drug effects.

Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (including SAPHRIS) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-marketing reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required additional medical treatment or monitoring. SAPHRIS should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

Use in lactation

Asenapine and/or its metabolites were excreted in the milk of rats during lactation. It is not known whether asenapine and/or its metabolites are excreted in human milk. It is recommended that women receiving SAPHRIS should not breast feed.

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 SAPHRIS therapy does not affect them adversely.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

SAPHRIS has been administered in clinical trials to approximately 4500 subjects, including more than 3150 patients in phase 2/3 trials with schizophrenia or manic episodes associated with bipolar I disorder. In the table below, all treatment-related adverse events that have an incidence of ≥ 2% have been listed from the phase 2/3 schizophrenia and bipolar mania trials (Table 2).

Table 2
Treatment – related adverse events for all phase 2/3 trials. Combined schizophrenia and bipolar disorder studies. (≥ 2%) (All subjects treated group)

System organ class Preferred term		Placebo n=1064	Asenapine 5 - 10mg bid n=3159	Olanzapine 5 - 20mg QD n=1139
Gastrointestinal disorders				
	Nausea	42 (3.9)	106 (3.4)	29 (2.5)
	Hypoaesthesia oral	5 (0.5)	103 (3.3)	3 (0.3)
	Dry Mouth	15 (1.4)	55 (1.7)	54 (4.7)
	Constipation	28 (2.6)	49 (1.6)	24 (2.1)

System organ class Preferred term		Placebo n=1064	Asenapine 5 - 10mg bid n=3159	Olanzapine 5 - 20mg QD n=1139
General disorders and administration site conditions				
	Fatigue	18 (1.7)	87 (2.8)	53 (4.7)
Investigations				
	Weight increased	6 (0.6)	239 (7.6)	212 (18.6)
	Alanine aminotransferase increased	6 (0.6)	37 (1.2)	23 (2.0)
Metabolism and nutrition disorders				
	Increased appetite	6 (0.6)	53 (1.7)	47 (4.1)
Nervous system disorders				
	Somnolence	21 (2.0)	339 (10.7)	113 (9.9)
	Sedation	36 (3.4)	237 (7.5)	140 (12.3)
	Akathisia	22 (2.1)	195 (6.2)	47 (4.1)
	Dizziness	29 (2.7)	131 (4.1)	50 (4.4)
	Headache	58 (5.5)	126 (4.0)	65 (5.7)
	Parkinsonism	10 (0.9)	100 (3.2)	15 (1.3)
	Tremor	13 (1.2)	70 (2.2)	14 (1.2)
Psychiatric disorders				
	Insomnia	57 (5.4)	207 (6.6)	47 (4.1)
	Anxiety	30 (2.8)	108 (3.4)	18 (1.6)
	Schizophrenia	27 (2.5)	87 (2.8)	21 (1.8)
	Agitation	25 (2.3)	76 (2.4)	15 (1.3)

bid = twice daily; QD = once daily

Metabolic changes, including hyperglycaemia and Diabetes Mellitus, dyslipidaemia and weight gain of >7% of total body weight, have been observed in adults exposed to SAPHRIS. See **Section 4.4 Special Warnings and Precautions for Use, Metabolic changes**.

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

The local anaesthetic properties of asenapine should be considered as a possible alternative etiology for the oropharyngeal symptoms.

Paediatric population
Asenapine is not approved for use in this population as the efficacy and safety has not been established.

SAPHRIS is not approved for use in subjects < 18 years of age. The incidence of dystonia in paediatric clinical trials using a gradual up-titration was similar to that seen in adult trials. Based on a small pharmacokinetic study, paediatric patients aged 10-17 years appeared to be more sensitive to dystonia when a gradual up-titration schedule was not followed. Metabolic changes, somnolence and sedation were more common in children compared to what has been observed in adults. For Metabolic Changes, see **Section 4.4 Special Warnings and Precautions for Use, Metabolic changes**.

Bipolar disorder

The safety of SAPHRIS was evaluated in 403 paediatric patients (ages 10-17 years) with manic or mixed episodes associated with bipolar I disorder who participated in a single, three-week, placebo-controlled, double-blind trial, of whom 302 patients received SAPHRIS at fixed doses ranging from 2.5 mg to 10 mg twice daily.

SAPHRIS is not approved for use in subjects < 18 years with bipolar 1 disorder.

The most common adverse reactions (≥5 % and at least twice the rate of placebo) were somnolence (31.3%-34.3%), sedation (15.4%-19.2%), dizziness (5.1% to 10.1%), dysgeusia (3.8%-9.1%), hypoaesthesia oral (17.3%-20.2%), paraesthesia oral (8.7%-11%), nausea (4.8%-6.1%), increased appetite (6.1%-9.6%), fatigue (3.8%-13.1%), and weight increased (2.0%-5.8%).

Eleven subjects (2.8%) developed new-onset Metabolic Syndrome, as defined by the International Diabetes Federation, compared to no subjects in placebo - see **Section 4.4 Special Warnings and Precautions for Use, Metabolic changes**.

Schizophrenia

The safety of SAPHRIS was also evaluated in an eight-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.

SAPHRIS is not approved for use for subjects < 18 years with schizophrenia.

The most common adverse reactions (proportion of patients ≥5 % and at least twice placebo) were somnolence (17.0%-20.4%), sedation (4.1%-11.3%), akathisia (4.1%-6.6%), dizziness (1.9%-7.1%), dysguesia (3.8%-9.1%) and hypoaesthesia oral (4.7%-5.1%). The number of patients with ≥7 % weight gain was significantly higher for asenapine 5 mg twice daily (13.1 %) compared to placebo (3.1%). Three subjects (1%) developed new-onset Metabolic Syndrome compared to no cases in placebo - see **Section 4.4 Special Warnings and Precautions for Use, Metabolic changes**.

Post-market experience

The following additional adverse reactions have been identified during post-marketing use of SAPHRIS. Because these reactions are reported voluntarily from a population of an uncertain size, it is generally not possible to reliably estimate their frequency.

Immune system disorders: serious hypersensitivity reactions, including anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue, dyspnea, wheezing and rash. In several cases, these reactions occurred after the first dose.

Gastrointestinal disorders: oral mucosal lesions (ulcerations, blistering and inflammation); salivary hypersecretion.

Psychiatric disorders: anxiety

Cardiac disorders: QT Interval Prolongation

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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 events 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 SAPHRIS. There is no specific antidote to SAPHRIS. The possibility of multiple drug 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 (adrenaline (epinephrine) and dopamine should not be used, since beta stimulations may worsen hypotension in the setting of SAPHRIS-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The mechanism of action of asenapine, as with other drugs having efficacy in schizophrenia and 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 D_2 and 5-HT_{2A} receptors. Actions at other receptors e.g., 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-HT_6, 5-HT_7, D_3, and α_2-adrenergic receptors, may also contribute to the clinical effects of asenapine.

Clinical trials

Schizophrenia

Acute Schizophrenia

The efficacy of SAPHRIS in the treatment of schizophrenia was investigated in three fixed-dose, short-term (6 weeks), randomised, double-blind, placebo- and active-controlled trials of patients who met DSM IV criteria for schizophrenia and were having an acute exacerbation of their schizophrenic illness. The primary efficacy rating scale was the Positive and Negative Syndrome Scale (PANSS), which assesses the symptoms of schizophrenia. Secondary efficacy endpoints included each of the PANSS subscales (PANSS positive, negative and general psychopathology subscales), the PANSS subscales based on the Marder factor analysis and the Clinical Global Impression (CGI). **Study 041004** was a trial (n=174) comparing SAPHRIS (5 mg twice daily) to placebo with risperidone (3 mg twice daily) as the active control. **Study 041023** was a trial (n=448) comparing two fixed doses of SAPHRIS (5 and 10 mg twice daily), to placebo with haloperidol (4 mg twice daily) as the active control. **Study 041021** was a trial (n=386) comparing two fixed doses of SAPHRIS (5 and 10 mg twice daily) to placebo with olanzapine (15 mg once daily) as the active control. The results for the efficacy variables (change from baseline in PANSS total score and 30% responder rates) are presented in the following tables.

Table 3
Study 041004

Variable	Placebo (N=60)	Asenapine 5mg bid (N=58)	Risperidone 3mg bid (N=56)
PANSS (Mean ± SE)			
Baseline	92.43 ± 1.93	96.48 ± 2.16	92.18 ± 2.05
Visit 6/Endpoint	87.17 ± 2.81	80.62 ± 2.79	81.25 ± 3.02
Endpoint Change	-5.27 ± 2.30	-15.86 ± 2.62	-10.93 ± 2.67
Difference in mean endpoint change from placebo		-10.59 p = 0.002	-5.66 p = 0.1186
PANSS Responders n (%)	15 (25)	22 (38)	22 (39)
Difference from placebo in responder rate		13%	14%

Table 4
Study 041023

Variable	Placebo (N=122)	Asenapine 5mg bid (N=109)	Asenapine 10mg bid (N=105)	Haloperidol 4mg bid (N=112)
PANSS (Mean + SD)				
Baseline	88.9 ± 11.67	89.2 ± 12.01	89.1 ± 12.88	88.6 ± 12.15
Endpoint	78.4 ± 19.88	73.3 ± 21.39	74.4 ± 20.42	73.5 ± 19.33
Endpoint Change (range)	-10.4 ± 18.05	-15.9 ± 17.69	-14.6 ± 19.31	-15.1 ± 16.29
Difference in mean endpoint change from placebo		-5.5 P = 0.029	-4.2 P = 0.068	-4.7 P = 0.0342
PANSS Responders n (%)	40 (32.8)	60 (55.0)	51 (48.6)	48 (42.9)
Difference from placebo in responder rate		22.2% P = 0.005	15.8% P = 0.015	10.1% P = 0.0927

Table 5
Study 041021

Variable	Placebo (N=93)	Asenapine 5mg bid (N=102)	Asenapine 10mg bid (N=96)	Olanzapine 15mg (N=95)
PANSS (Mean ± SD)				
Baseline	94.6 ± 12.69	91.7 ± 15.47	94.4 ± 13.58	93.7 ± 12.93
Endpoint	83.8 ± 19.82	78.1 ± 19.63	81.3 ± 20.13	78.0 ± 18.01
Endpoint Change (range)	-10.7 ± 17.00	-13.7 ± 17.24	-13.1 ± 18.49	-15.7 ± 16.15

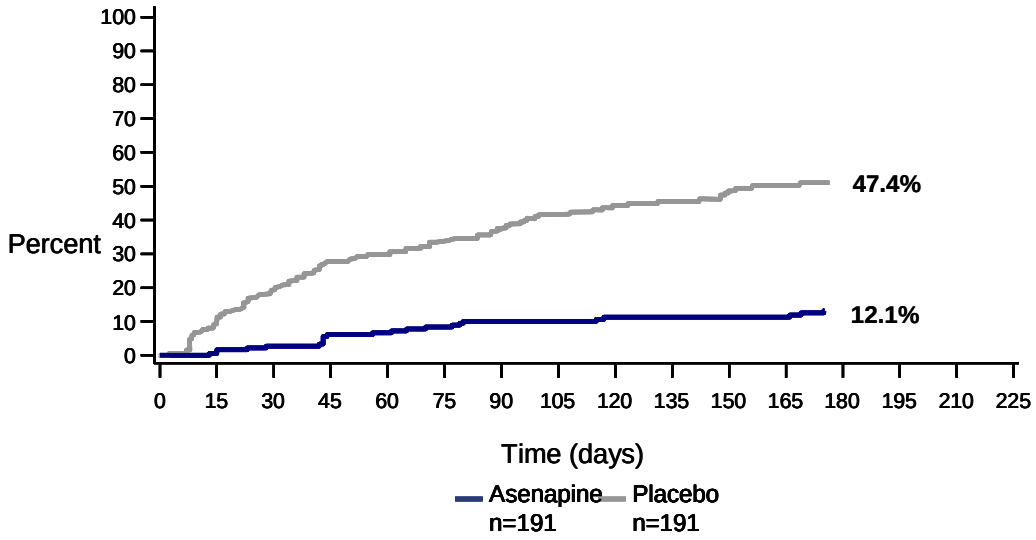
Difference in mean endpoint change from placebo		-3.0 p = 0.1278	-2.4 p = 0.3046	-5.0 p = 0.0168
PANSS Responders n (%)	21 (22.6)	39 (38.2)	33 (34.4)	39 (41.1)
Difference from placebo in responder rate		15.6% p = 0.0199	11.8% p = 0.0796	18.5% p = 0.0019

Maintenance in Schizophrenia

Study A7501012. This study was a randomized, placebo-controlled, double-blind, multicentre, multinational clinical trial evaluating the efficacy and safety of sublingually administered SAPHRIS (5 or 10 mg twice daily) compared to placebo in the prevention of relapse in subjects with schizophrenia. A total of 700 patients entered the open-label treatment with SAPHRIS for up to 26 weeks. Of these, a total of 386 patients met criteria for stabilization on SAPHRIS and were randomised to treatment in the 26-week double-blind placebo-controlled phase of the trial.

SAPHRIS was significantly more effective than placebo in preventing relapse, as measured by the endpoint of the trial estimated through Kaplan-Meier curves. At the 26 week endpoint, 47% of the placebo-treated patients relapsed, compared with only 12% of the asenapine-treated patients (p<0.0001) (Figure 1).

Figure 1
Kaplan-Meier estimation of percent relapse/impending relapse as determined by the investigator (Intent-to-treat)



Bipolar 1 disorder

Acute treatment of manic or mixed episodes

Two similarly designed 3-week, randomised, double-blind, placebo and active-controlled (olanzapine) monotherapy trials involving 488 (Study A751004) and 489 (Study A751005) patients, respectively, with acute manic or mixed episode of bipolar I disorder with or without psychotic features, investigated the efficacy of SAPHRIS compared to placebo in the reduction of manic symptoms over 3 weeks. The primary efficacy end point was the reduction from baseline in YMRS mean change from BL score and for SAPHRIS a statistically significant

effect was noted as early as Day 2, and was maintained until the last trial visit (Day 21) when compared to placebo. The main efficacy results are presented in the following tables.

Table 6
Efficacy results (LOCF-ITT) for Study A751005

YMRS mean change from BL score	Placebo (n=103)	Asenapine (n=189)	Olanzapine (n=188)
Day 21			
LS mean change from baseline (SE)	- 5.5 (1.01)	- 10.8 (0.75)[a]	- 12.6 (0.76)[a]
% responders	25.2	42.3[b]	50.0[a]
% remitters	22.3	40.2[c]	39.4[d]

Responders: a 50% decrease from baseline in YMRS total score
Remitters: have a YMRS total score of 12 or lower
[a] P < 0.0001; [b] P = 0.0049, [c] P = 0.0020; [d] P = 0.0041 (all compared to placebo)

Table 7
Efficacy results (LOCF-ITT) for Study A751004

YMRS mean change from BL score	Placebo (n=94)	Asenapine (n=183)	Olanzapine (n=203)
Day 21			
LS mean change from baseline (SE)	- 7.8 (1.11)	- 11.5 (0.80)[b]	- 14.6 (0.76)[a]
% responders	34.0	42.6	54.7[c]
% remitters	30.9	35.5	46.3[d]

Responders: a 50% decrease from baseline in YMRS total score
Remitters: have a YMRS total score of 12 or lower
[a] P < 0.0001; [b] P = 0.0065, [c] P = 0.0011; [d] P = 0.0159 (all compared to placebo)

Maintenance of Effect:

A 9-week extension trial (Study A751006; n=181 for asenapine and n=229 for olanzapine) was conducted to demonstrate non-inferiority of the maintenance of effectiveness of SAPHRIS compared with olanzapine for up to 12 weeks. The primary efficacy endpoint was the change from baseline YMRS score to week 12. SAPHRIS was shown not to be statistically (PP: 1.1 with 95% CI -0.47 to 2.78; ITT: 1.2 with 95% CI -0.42 to 2.81) inferior to olanzapine in the treatment of subjects with a manic or mixed bipolar episode.

Combination therapy with lithium or sodium valproate

A 12-week randomised, double-blind, placebo-controlled, flexible dose trial (Study A751008) examined the efficacy of SAPHRIS (5 mg as the starting dose with the option to uptitrate to 10 mg) when administered concurrently with lithium or sodium valproate compared with lithium or sodium valproate monotherapy. The primary efficacy endpoint was the change from baseline to Day 21 (3 weeks) in the YMRS score (LOCF-ITT). Multiple secondary parameters were investigated including YMRS responder and remitter rates. The results are presented below up to 84 days (12 weeks) of treatment (Table 8).

Table 8
Efficacy results (LOCF-ITT) for asenapine combination therapy with lithium or sodium valproate in comparison with lithium or sodium valproate monotherapy (Study A751008)

YMRS mean change from BL score	Placebo (n=163)	Asenapine (n=155)	p-value
Day 21			
LS mean change from baseline (SE)	- 7.9 (0.76)	- 10.3 (0.79)	0.0257
% responders	27.0	34.2	0.1634

% remitters	21.5	33.5	0.0158
Day 84			
LS mean change from baseline (SE)	- 9.3 (0.89)	-12.7 (0.92)	0.0073
% responders	34.4	47.7	0.0152
% remitters	30.1	43.2	0.0148

Responders: a 50% decrease from baseline in YMRS total score
Remitters: have a YMRS total score of 12 or lower

The efficacy of combination therapy beyond 12 weeks has not been demonstrated.

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 average peak plasma concentrations at steady state of 5 and 10 mg twice daily were 3.6 ng/mL and 7.0 ng/mL respectively. The absolute bioavailability of sublingual asenapine at 5 mg is 35%. 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 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 Dose and Method of Administration**).

Distribution

Asenapine is rapidly distributed and has a large volume of distribution (approximately 1700 L), indicating extensive extravascular distribution. Asenapine is highly bound (95-97% at 1-500 ng/mL) to plasma proteins *in vitro,* including albumin and α_1-acid glycoprotein.

Metabolism

Asenapine is extensively metabolised. Oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP 1A2) and direct glucuronidation by UGT1A4 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. SAPHRIS activity is primarily due to the parent drug.

Asenapine is a weak inhibitor of microsomal CYP2D6 activity. Asenapine does not cause induction of CYP1A2 activity and slightly increased CYP3A4 activity at high concentrations in cultured human hepatocytes. Coadministration 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 Interactions with Other Medicines and Other Forms of Interactions**).

Excretion

Asenapine is a high clearance drug, 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 drug. Following an initial more rapid distribution phase, the terminal half-life of asenapine is approximately 24 hours. Steady-state concentrations of asenapine are reached within 3 days of twice daily dosing. Overall, steady-state asenapine pharmacokinetics are similar to single-dose pharmacokinetics.

Special populations

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.

Hepatic insufficiency
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 Dose and Method of Administration, Hepatic impairment**).

Elderly
Interim results from 33 subjects aged 65-85 years indicate approximately 30% higher exposure to asenapine in elderly patients compared to adult patients.

Paediatric patients (10-17 years of age)
Asenapine is rapidly absorbed with C_{max} occurring approximately at 1.5 hours (0.5-3 hours) and an initial rapid decline in plasma concentrations is followed by a slower elimination phase. Asenapine exposure increases in a dose-proportional manner over the range of 1 to 10 mg twice daily. Steady-state is achieved within 6-8 days of twice daily dosing and the mean terminal half-life is approximately 20 hours (range: 16-25 hours). Population pharmacokinetic analysis of asenapine in paediatric patients suggests that age, gender, BMI and race have no clinically meaningful effect on the pharmacokinetics of asenapine.

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.

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

Race
A single dose pharmacokinetic study did not demonstrate any significant differences in pharmacokinetic parameters between Japanese and Caucasian healthy subjects. Additionally, in a population pharmacokinetic analysis, no clinically relevant effects of race on the pharmacokinetics of asenapine were found.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Asenapine was not genotoxic in *in vitro* (bacterial reverse mutation, mammalian cell forward mutation, chromosomal aberration, sister chromatid exchange) and *in vivo* (rat micronucleus) tests.

Carcinogenicity

Long term carcinogenicity studies with subcutaneous administration were conducted in mice and rats. Doses used resulted in estimated drug exposures (based on plasma AUC) that were up to 3-4 fold the expected human value with the maximum recommended dose. No oncogenic responses to asenapine treatment were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each wafer of SAPHRIS contains gelatin and mannitol.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the ARTG.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Protect from light and moisture.

Store in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

SAPHRIS is available in Al/Al blister packs of 20, 60 and 100 wafers.

Not all pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Saphris is a novel antipsychotic, belonging to the dibenzo-oxepino pyrroles. It has antagonist activity on the dopamine 2 (D_2) and serotonin (5-HT)-2A receptors.

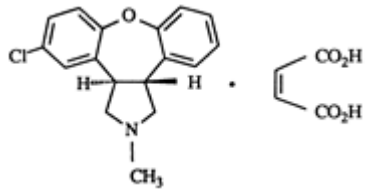
Asenapine maleate is chemically identified as (3a*R*,12b*R*)-rel-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1*H*-dibenz(2,3:6,7)oxepino[4,5-c]pyrrole (2*Z*)-2-butenedioate (1:1)

Molecular formula: $C_{17}H_{16}ClNO \cdot C_4H_4O_4$ (and enantiomer)

Molecular weight: 401.84

The solubility of asenapine (active entity) in water is 3.7 mg/mL, in 0.1M HCl is 13 mg/mL and in aqueous buffers of pH 4.0 and 7.0 the solubility is 3.8 mg/mL and 3.0 mg/mL, respectively. The pKa of asenapine is 8.6 (determined in water/methanol). Asenapine has a log P (n-octanol/water) of 4.9 for the neutral species and 1.4 for the cationic species.

Chemical structure
Asenapine maleate has the following structural formula:



CAS number

85650-56-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

Organon Pharma Pty Ltd

Building A, 26 Talavera Road

Macquarie Park NSW 2113

9 DATE OF FIRST APPROVAL

7 March 2011

10 DATE OF REVISION

21 December 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Amendment of sponsor details to reflect sponsor transfer

RCN000006067, RCN000005108