

PRODUCT MONOGRAPH

 **SAPHRIS[®]**

(asenapine sublingual tablets)

5 mg and 10 mg asenapine, as asenapine maleate

Antipsychotic

Manufactured by:
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Date of Revision:
April 27, 2021

Submission Control No: 250558

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(asenapine sublingual tablets)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Sublingual	Tablet/ 5 mg , 10 mg	Gelatin, mannitol.

INDICATIONS AND CLINICAL USE

Adults:

Schizophrenia

SAPHRIS[®] (asenapine) sublingual tablet is indicated for the treatment of schizophrenia.

Bipolar Disorder

SAPHRIS[®] is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder. SAPHRIS[®] may be used as acute monotherapy or co-therapy with lithium or divalproex sodium (see Part II: CLINICAL TRIALS).

Physicians who elect to use SAPHRIS[®] for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Geriatrics (≥ 65 years of age):

See WARNINGS AND PRECAUTIONS – Serious Warnings and Precautions Box and Special populations.

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 WARNINGS AND PRECAUTIONS, Special populations, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions.)

Pediatrics (<18 years of age):

The safety and efficacy of SAPHRIS® have not been established in pediatric populations. SAPHRIS® is not indicated in pediatric patients and its use is not recommended. (See WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics; ADVERSE REACTIONS, Pediatrics and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions.)

CONTRAINDICATIONS

Hypersensitivity reactions, including anaphylaxis and angioedema, have been observed in patients treated with asenapine. Therefore, SAPHRIS® is contraindicated in patients with a known hypersensitivity to this drug or to any ingredient in the formulation. (See WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Increased Mortality in Elderly Patients with Dementia

Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6 fold increase in death rate in the drug-related patients. 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 (see WARNINGS AND PRECAUTIONS, Special Populations, Use in Geriatric Patients with Dementia).

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have been observed in patients treated with asenapine. In several cases, these reactions occurred after the first dose. These hypersensitivity reactions included: anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue, dyspnea, wheezing and rash. Patients should be informed of the signs and symptoms of a serious allergic reaction (e.g., difficulty breathing, itching, swelling of the face, tongue, throat, or feeling lightheaded etc.). Patients should be instructed to seek immediate emergency assistance if they develop any of these signs and symptoms.

General

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 SAPHRIS[®]. 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 medication with anticholinergic activity, or being subject to dehydration.

Falls: Asenapine may cause adverse effects such as somnolence, orthostatic hypotension, motor and sensory instability, dizziness and extrapyramidal symptoms, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Carcinogenesis and Mutagenesis

For animal data, see Part II: TOXICOLOGY section.

Cardiovascular

QT interval: The effects of SAPHRIS[®] on the QT/QTc interval were evaluated in a dedicated QT study. This trial involved SAPHRIS[®] 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, SAPHRIS[®] 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 measurements, 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 SAPHRIS[®] and placebo in these short-term trials. There were no reports of Torsade de Pointes or any other adverse reactions associated with delayed ventricular repolarization.

The use of SAPHRIS[®] should be avoided in combination with other drugs known to prolong QTc including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and antibiotics (e.g., gatifloxacin, moxifloxacin). SAPHRIS should also be avoided in patients with a history of cardiac arrhythmias and in other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including bradycardia; hypokalemia or hypomagnesemia; and presence of congenital prolongation of the QT interval.

Orthostatic Hypotension and Syncope: SAPHRIS[®] may induce orthostatic hypotension and syncope, especially early in treatment, probably reflecting its α 1-adrenergic antagonist

properties. Elderly patients are particularly at risk for experiencing orthostatic hypotension. In short-term schizophrenia trials, syncope was reported in 0.2% (1/572) of patients treated with therapeutic doses (5 or 10 mg twice daily) of asenapine, compared to 0.3% (1/378) of patients treated with placebo. In short-term bipolar mania trials, syncope was reported in 0.3% (1/379) of patients treated with therapeutic doses (5 mg or 10 mg twice daily) of asenapine, compared to 0% (0/203) of patients treated with placebo.

Patients should be instructed about non-pharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position).

SAPHRIS[®] should be used with caution in elderly patients and 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, and treatment with antihypertensive medications).

Dependence/Tolerance

SAPHRIS[®] has not been systematically studied in animals or humans for its abuse potential or its ability to induce tolerance or physical dependence. Thus, it is not possible to predict the extent to which a CNS-active drug will be misused, diverted and/or abused once it is marketed. Patients should be evaluated carefully for a history of drug abuse, and such patients should be observed carefully for signs that they are misusing or abusing SAPHRIS[®] (e.g., drug-seeking behavior, increases in dose).

Endocrine and Metabolism

Hyperglycaemia and Diabetes Mellitus:

Hyperglycaemia or exacerbation of pre-existing diabetes has occasionally been reported during treatment with asenapine. Diabetic ketoacidosis (DKA) has occurred in patients treated with antipsychotics with no reported history of hyperglycemia. Therefore, patients should have baseline and periodic monitoring of blood glucose and body weight.

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. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include SAPHRIS[®], suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic

treatment despite discontinuation of the antipsychotic drug. 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. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Hyperprolactinemia: Like other drugs that antagonize dopamine D2 receptors, SAPHRIS® can elevate prolactin levels, and the elevation can persist during chronic administration. Hyperprolactinemia 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. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. In primarily short term asenapine clinical trials, there were few adverse events related to abnormal prolactin levels reported. (See also ADVERSE REACTIONS, Prolactin)

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 epidemiologic 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.

Weight Gain:

Increases in weight have been observed in pre-marketing clinical trials with SAPHRIS® (see ADVERSE REACTIONS, Weight Gain). Weight gain does not appear to be dose-related, but a potential relation to baseline weight cannot be excluded, as below.

In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia or schizoaffective disorder, the proportion of patients with a $\geq 7\%$ increase in body weight (at Endpoint) was 14.7%. The mean weight gain from baseline was 0.9 kg. Table 1 provides the mean weight change from baseline and the proportion of patients with a weight gain of $\geq 7\%$ categorized by Body Mass Index (BMI) at baseline.

Table 1: Weight Change Results Categorized by BMI at Baseline: Comparator-Controlled 52-Week Study in Schizophrenia

	BMI < 23 SAPHRIS® N=295	BMI 23 - ≤ 27 SAPHRIS® N=290	BMI > 27 SAPHRIS® N=302
Mean change from Baseline (kg)	1.7	1	0
% with $\geq 7\%$ increase in body weight	22 %	13 %	9 %

Gastrointestinal

Antiemetic Effect: Drugs that have dopamine antagonist effects may have an antiemetic effect. Such an effect may mask signs of toxicity due to overdosage of other drugs, or may mask symptoms of disease such as brain tumour or intestinal obstruction.

Genitourinary

Rare cases of priapism have been reported with antipsychotic use, such as with SAPHRIS[®] (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hematologic

Leukopenia, Neutropenia, and Agranulocytosis: In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally 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 (CBC) monitored frequently during the first few months of therapy and SAPHRIS[®] should be discontinued at the first sign 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 $<1.0 \times 10^9/L$ should discontinue SAPHRIS[®] and have their WBC followed until recovery.

Venous thromboembolism: Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs, including SAPHRIS[®], in case reports and/or observational studies. When prescribing SAPHRIS[®] all potential risk factors for VTE should be identified and preventative measures undertaken.

Hepatic/Biliary/Pancreatic

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.

Immune

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):

Post market cases of DRESS have been reported in association with similar atypical antipsychotic drugs within the class.

Neurologic

Neuroleptic Malignant Syndrome: Neuroleptic Malignant Syndrome (NMS) is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs, including SAPHRIS®.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.), and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include 1) immediate discontinuation of all antipsychotic drugs including SAPHRIS® and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential re-introduction of therapy should be very carefully considered. The patient should be carefully monitored, since recurrence of NMS has been reported.

Tardive Dyskinesia: A syndrome of potentially irreversible, involuntary, dyskinetic movements can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome.

The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SAPHRIS® should be prescribed in a manner that is most likely to minimize the occurrence of TD. Chronic antipsychotic treatment should generally be reserved for patients who suffer from 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.

If signs and symptoms of tardive dyskinesia appear in a patient on SAPHRIS[®], drug discontinuation should be considered. However, some patients may require treatment with SAPHRIS[®] despite the presence of the syndrome.

Seizures: In clinical trials, cases of seizure were occasionally reported during treatment with SAPHRIS[®]. Therefore, as with other antipsychotic drugs, SAPHRIS[®] should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

Potential for Cognitive and Motor Impairment:

In short-term, fixed-dose, placebo-controlled schizophrenia trials, somnolence (including sedation) was reported in 15% (41/274) of patients on SAPHRIS[®] 5 mg twice daily and in 13% (26/208) of patients on SAPHRIS[®] 10 mg twice daily compared to 7% (26/378) of placebo patients. In short-term, placebo-controlled bipolar mania trials somnolence was reported in 24% of patients on SAPHRIS[®] compared to 6% of placebo patients. Somnolence (including sedation) led to discontinuation in 0.6% of patients in short-term, placebo-controlled trials.

As with other antipsychotics, patients should be cautioned about operating machinery, including motor vehicles, until they are reasonably certain that SAPHRIS[®] therapy does not affect them adversely.

Psychiatric

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

Renal

No dosage adjustment is required for patients with renal impairment.

Special Populations

Pregnant Women:

Teratogenic Effects

There are no adequate data from the use of SAPHRIS[®] in pregnant women. Maternal and embryo-fetal toxic effects were found in animal studies (see Part II: TOXICOLOGY). SAPHRIS[®] should not be used during pregnancy unless clearly necessary and only if the potential benefit outweighs the potential risk to the foetus.

Non-Teratogenic Effects

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been 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 intensive care unit support and prolonged hospitalization.

SAPHRIS[®] should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

Nursing Women: 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 SAPHRIS[®] should not breast feed.

Pediatrics (< 18 years of age): The safety and efficacy of SAPHRIS[®] has not been established in pediatric populations. SAPHRIS[®] is not indicated in pediatric patients and its use is not recommended. (See ADVERSE REACTIONS, Pediatrics and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). SAPHRIS[®] failed to meet primary efficacy objectives in a pediatric schizophrenia trial.

Weight gain has been observed with atypical antipsychotic use in pediatric and adolescent patient populations. Independent of any drug-specific effects, weight gain can be associated with adverse changes in other metabolic parameters (e.g., glucose and lipid metabolism). Abnormal childhood weight and metabolic status can have adverse effects on cardiovascular outcomes in adulthood. Weight gain and adverse effects on other metabolic parameters associated with atypical antipsychotics can be more frequent or more severe in pediatric and adolescent patients than in the adult patients.

In trials, mean weight and BMI change and the incidence of clinically significant weight gain at endpoint ($\geq 7\%$) were greater in asenapine-treated patients compared to placebo. Based on the criteria defined per the International Diabetes Federation (IDF), new onset metabolic syndrome was identified if subjects who did not meet IDF criteria for metabolic syndrome at baseline met 3/5 criteria including obesity at any visit during treatment or endpoint. There were a greater number of patients who met criteria for new onset of Metabolic Syndrome (MBS) in the asenapine treatment groups compared to placebo.

The following adverse events in the two studies in pediatrics are of note because they are not typical of the adult population treated with asenapine: sedation, parkinsonism, abdominal pain, paraesthesia oral, nausea, glossodynia, anger, suicidal ideation, dehydration, irritability, blood insulin increase, AST increased, muscle strain, rash, myalgia, tachycardia, seasonal allergy, epistaxis, and acne. There are also adverse events of note due to a greater incidence rate compared to adults, or a greater differential over placebo: Sedation, somnolence, EPS, dystonia weight increased, increased appetite.

Paediatric patients appeared to be more sensitive to dystonia with initial dosing with asenapine when a gradual up-titration schedule was not followed.

The long-term safety, including cardiometabolic effects and effects on growth, maturation and behavioural development in patients under 18 years of age has not been systematically evaluated.

Geriatrics (≥ 65 years of age): There is limited data on safety and efficacy in patients 65 years of age or older. In addition, as this population has more frequent hepatic, renal, central nervous system, and cardiovascular dysfunctions, and more frequent use of concomitant medication, caution should be exercised with the use of SAPHRIS[®] in the elderly patient.

Currently available pharmacokinetic data are described in ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions.) See also WARNINGS AND PRECAUTIONS – Serious Warnings and Precautions Box and Special populations.)

Use in Geriatric Patients with Dementia:

Overall Mortality

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. In a meta-analysis of 13 placebo-controlled trials of various atypical antipsychotic drugs, elderly patients with dementia treated with atypical antipsychotic drugs, which did not include SAPHRIS[®], showed increased mortality compared to placebo. SAPHRIS[®] is not indicated for the treatment of patients with dementia-related psychosis.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Cases of dysphagia were occasionally reported in patients treated with SAPHRIS[®].

Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SAPHRIS[®] and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Cerebrovascular Adverse Events (CVAEs), Including Stroke in Elderly Patients with Dementia

In placebo-controlled trials with some atypical antipsychotics, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. There are insufficient data with asenapine to know if there is an increased risk of cerebrovascular events associated with asenapine. SAPHRIS[®] is not indicated for the treatment of patients with dementia-related psychosis (see also WARNINGS AND PRECAUTIONS).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Sublingual asenapine has been administered in clinical trials to approximately 4500 subjects, including more than 3150 patients in phase 2/3 trials with schizophrenia or manic or mixed episodes associated with bipolar I disorder.

Adverse reactions were defined as treatment-emergent adverse events that were considered to be reasonably associated with the use of SAPHRIS[®] based on the comprehensive assessment of the available adverse event information. A causal association for SAPHRIS[®] often cannot be reliably established in individual cases.

The stated frequencies of adverse events represent the proportion of individuals who reported at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; i.e. all events meeting the defined criteria, regardless of investigator causality are included.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Reactions Associated with Discontinuation of Treatment, in Patients with Schizophrenia

In short-term, placebo-controlled trials, a total of 9% of SAPHRIS[®]-treated subjects and 10% of placebo subjects discontinued treatment due to adverse reactions. There were no drug-related adverse reactions associated with discontinuation in subjects treated with SAPHRIS[®] at the rate of at least 1% and at least twice the placebo rate.

Adverse Reactions Associated with Discontinuation of Treatment, in Patients with Bipolar Manic or Mixed Episode

Approximately 10% of SAPHRIS[®]-treated subjects in short-term, placebo-controlled monotherapy trials discontinued treatment due to an adverse reaction, compared with about 6% on placebo. The most common adverse reactions associated with discontinuation in subjects treated with SAPHRIS[®] (rates at least 1% and at least twice the placebo rate) were anxiety (1.1%) and oral hypoesthesia (1.1%) compared to placebo (0%).

In combination therapy trials (with lithium or valproate), approximately 16% of SAPHRIS[®]-treated patients discontinued treatment due to an adverse reaction, compared with about 11% on placebo. The most common adverse reactions associated with discontinuation in subjects treated with SAPHRIS[®] (rates at least 1% and at least twice the placebo rate) were depression (2.5%), suicidal ideation (2.5%), bipolar I disorder (1.9%), insomnia (1.9%) and depressive symptoms (1.3%).

Commonly Observed Adverse Events in Short-Term Placebo-Controlled Clinical Trials

The most common adverse reactions ($\geq 5\%$ and at least twice the rate of placebo) reported with asenapine in acute treatment of schizophrenia were akathisia, oral hypoesthesia, and somnolence. The most common adverse reactions ($\geq 5\%$ and at least twice the rate of placebo) reported with acute monotherapy treatment of manic or mixed episodes associated with bipolar I disorder were

somnolence, dizziness, extrapyramidal symptoms other than akathisia, and weight increased, and during the combination therapy trial were somnolence and oral hypoesthesia.

Adverse Events Reported in Schizophrenia Short-Term Placebo-Controlled Trials

TABLE 2: Adverse Reactions Reported in 2% or More of Subjects in One of the SAPHRIS® Dose Groups and Which Occurred at Greater Incidence Than in the Placebo Group in 6-Week Schizophrenia Trials

System Organ Class/ Preferred Term	Placebo N=378	SAPHRIS 5 mg twice daily N=274	SAPHRIS 10 mg twice daily N=208	All SAPHRIS§ 5 mg or 10 mg twice daily N=572
Gastrointestinal disorders				
Constipation	6%	7%	4%	5%
Dry mouth	1%	3%	1%	2%
Oral hypoesthesia	1%	6%	7%	5%
Salivary hypersecretion	0%	<1%	4%	2%
Stomach discomfort	1%	<1%	3%	2%
Vomiting	5%	4%	7%	5%
General disorders				
Fatigue	3%	4%	3%	3%
Irritability	<1%	2%	1%	2%
Investigations				
Weight increased	<1%	2%	2%	3%
Metabolism disorders				
Increased appetite	<1%	3%	0%	2%
Nervous system disorders				
Akathisia*	3%	4%	11%	6%
Dizziness	4%	7%	3%	5%
Extrapyramidal symptoms (excluding akathisia)†	7%	9%	12%	10%
Somnolence‡	7%	15%	13%	13%
Psychiatric disorders				
Insomnia	13%	16%	15%	15%
Vascular disorders				
Hypertension	2%	2%	3%	2%

*Akathisia includes: akathisia and hyperkinesia.

†Extrapyramidal symptoms included dystonia, oculogyration, dyskinesia, tardive dyskinesia, muscle rigidity, parkinsonism, tremor, and extrapyramidal disorder (excluding akathisia).

‡Somnolence includes the following events: somnolence, sedation, and hypersomnia.

§Also includes the Flexible-dose trial (N=90).

Dose-Related Adverse Reaction

Of all the adverse reactions listed in Table 2, the only apparent dose-related adverse reactions were akathisia and parkinsonism.

Adverse Events Reported in Bipolar Mania Short-Term Placebo-Controlled Trials (Monotherapy Treatment)

The database for Bipolar 1 Disorder (monotherapy treatment) consists of a total of three placebo-controlled 3-week trials: 2 similarly-designed flexible-dose studies (10 mg BID with flexibility to decrease), and a subsequent fixed dose study (5 mg BID and 10 mg BID). Table 3 enumerates the incidence of treatment-emergent adverse events associated with the use of SAPHRIS® in both flexible and fixed dose trials.

TABLE 3: Adverse Reactions Reported in 2% or More of Subjects in One of the SAPHRIS® Dose Groups and Which Occurred at a Greater Incidence Than in the Placebo Group in 3-Week Bipolar Mania Trials (two flexible dose trials, and one fixed-dose)

System Organ Class/ Preferred Term	Placebo (N=329, combined)	SAPHRIS 5 or 10 mg BID flexible dose* (N=379)	SAPHRIS 5 mg BID (N=122)	SAPHRIS 10 mg BID (N=119)
Gastrointestinal disorders				
Abdominal pain/discomfort [†]	1%	2%	2%	3%
Dry mouth	2%	3%	3%	<1%
Dyspepsia	3%	4%	4%	5%
Hypoaesthesia oral	<1%	4%	12%	23%
Toothache	2%	3%	2%	2%
Vomiting	3%	4%	<1%	3%
General disorders				
Fatigue	2%	4%	2%	4%
Infections and infestations				
Nasopharyngitis	1%	2%	0%	3%
Injury, poisoning and procedural complications				
Arthropod bite	0%	<1%	0%	3%
Investigations				
Alanine aminotransferase increased	0%	<1%	0%	3%
Weight increased	<1%	5%	0%	<1%
Metabolism disorders				
Increased appetite	2%	4%	<1%	6%
Musculoskeletal and connective tissue disorders				
Arthralgia	<1%	3%	<1%	2%
Pain in extremity	<1%	2%	0%	<1%
Nervous system disorders				
Akathisia	2%	4%	4%	15%
Dizziness	4%	11%	3%	5%
Dysgeusia	<1%	3%	3%	9%
Headache	10%	12%	7%	5%

System Organ Class/ Preferred Term	Placebo (N=329, combined)	SAPHRIS 5 or 10 mg BID flexible dose* (N=379)	SAPHRIS 5 mg BID (N=122)	SAPHRIS 10 mg BID (N=119)
Oromandibular dystonia	0%	0%	2%	4%
Other extrapyramidal symptoms (excluding akathisia)‡	3%	7%	2%	2%
Somnolence§	5%	24%	20%	26%
Psychiatric disorders				
Agitation	3%	4%	4%	3%
Anxiety	2%	4%	0%	3%
Bipolar disorder	<1%	<1%	2%	0%
Depression	1%	2%	0%	<1%
Insomnia	5%	6%	4%	3%
Mania	4%	5%	4%	3%

* SAPHRIS 5 mg to 10 mg twice daily with flexible dosing.

† Abdominal pain/discomfort includes the following events: abdominal pain and abdominal discomfort.

‡ Extrapyramidal symptoms include the following events: dystonia, blepharospasm, torticollis, dyskinesia, tardive dyskinesia, muscle rigidity, parkinsonism, gait disturbance, masked facies and tremor (excluding akathisia).

§ Somnolence includes the following events: somnolence, sedation and hypersomnia.

**Adverse Events Reported in Bipolar Mania Short-Term Placebo-Controlled Trials
(Combination Therapy)**

TABLE 4: Adverse Reactions Reported in 2% or More Among SAPHRIS®-Treated (combination therapy) Bipolar Mania Patients and Which Occurred at Greater Incidence Than in the Placebo Group in 12 week Flexible-dose Trial:

System Organ Class/Preferred Term	Placebo N=166	SAPHRIS 5 mg or 10 mg twice daily* N=158
Eye disorders		
Vision blurred	<1%	3%
Gastrointestinal disorders		
Dyspepsia	2%	3%
Oral hypoesthesia	<1%	6%
Vomiting	1%	4%
General disorders		
Edema peripheral	<1%	3%
Fatigue	3%	4%
Irritability	2%	3%
Infections and infestations		
Nasopharyngitis	<1%	3%
Investigations		
Weight increased	<1%	5%

System Organ Class/Preferred Term	Placebo N=166	SAPHRIS 5 mg or 10 mg twice daily* N=158
Musculoskeletal and connective tissue disorders		
Arthralgia	0%	3%
Nervous system disorders		
Dizziness	3%	5%
Other extrapyramidal symptoms (excluding akathisia) [†]	7%	9%
Somnolence [‡]	10%	24%
Psychiatric disorders		
Agitation	5%	6%
Depression	3%	4%
Insomnia	10%	13%
Suicidal ideation	1%	4%
Skin and subcutaneous tissue disorders		
Pruritis	<1%	3%
Vascular disorders		
Hypertension	<1%	3%

* SAPHRIS[®] 5 mg to 10 mg twice daily with flexible dosing.

[†]Extrapyramidal symptoms included: dystonia, parkinsonism, oculogyration, and tremor (excluding akathisia).

[‡]Somnolence includes the following events: somnolence and sedation.

Long-term treatment with asenapine did not reveal any clinically relevant differences in the safety profile compared to the short-term trials, with the exception of weight gain (see WARNINGS AND PRECAUTIONS, Weight Gain).

Extrapyramidal Symptoms (EPS)

From the EPS-related events reported in the fixed-dose placebo-controlled short-term trials (6 weeks) for schizophrenia and 3 weeks for bipolar mania, there appears to be a dose-response relationship for akathisia and parkinsonism in patients treated with asenapine.

With respect to data objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), on the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias), in the short-term placebo-controlled schizophrenia and bipolar mania trials: The mean change from baseline for the all-SAPHRIS[®] 5 mg or 10 mg twice daily treated group was comparable to placebo in each of the rating scale scores.

With respect to the rates of akathisia in the short-term placebo-controlled trials: in the schizophrenia trials, the fixed-dose rates were 11% for 10 mg BID, 4% for 5 mg BID and 3% for placebo; in the fixed-dose bipolar mania trial, the rates were 15% for 10 mg BID, 4% with 5 mg BID and 1% for placebo. With respect to the rates of reported EPS-related events excluding akathisia: in the fixed schizophrenia trials, the rates were: 12% for 10 mg BID, 9% for 5 mg BID and 7% for placebo; in the flexible-dose bipolar mania trials, the rates were 7% for drug vs 2% for placebo.

Dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

For patients presenting with symptoms involving the tongue and throat, serious hypersensitivity reactions should also be considered (see WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions; ADVERSE REACTIONS, Post-market Adverse Events).

Weight Gain

In short-term schizophrenia and bipolar mania trials, there were differences in mean weight gain between SAPHRIS[®]-treated and placebo-treated patients. Weight gain does not appear to be a dose-related event. (See also WARNINGS AND PRECAUTIONS, Weight gain)

In short-term, 6-week placebo-controlled schizophrenia trials, the mean weight gain was 1.1 kg for SAPHRIS[®]-treated patients compared to 0.1 kg for placebo-treated patients. The proportion of patients with a $\geq 7\%$ increase in body weight (at Endpoint) was 5% for SAPHRIS[®]-treated patients versus 2% for placebo-treated patients.

In short-term, 3 week, flexible-dose, placebo-controlled bipolar mania trials, the mean weight gain for SAPHRIS[®]-treated patients was 1.3 kg compared to 0.2 kg for placebo-treated patients. The proportion of patients with a $\geq 7\%$ increase in body weight (at Endpoint) was 7% for SAPHRIS[®]-treated patients versus 1% for placebo-treated patients.

Oral hypoesthesia and oral paresthesia

Asenapine has anesthetic properties. Oral hypoesthesia and oral paresthesia may occur directly after administration and usually resolve within 1 hour.

For patients presenting with oropharyngeal symptoms, serious hypersensitivity reactions should also be considered (see WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions; ADVERSE REACTIONS, Post-market Adverse Events).

Constipation

Patients should be advised of the risk of severe constipation during SAPHRIS[®] treatment, and they should tell their doctor if constipation occurs or worsens, since they may need medical intervention.

Adverse Events in Pediatrics (<18 years of age)

The safety and efficacy of SAPHRIS® in children under the age of 18 years have not been established and its use is not recommended (see WARNINGS and PRECAUTIONS, Special Populations, Pediatrics). All of the adverse events described above for adults with bipolar disorder and schizophrenia should be considered in the case of children and adolescents taking SAPHRIS®. Additional adverse events of note from each of the two studies in the pediatric population, are summarized in the following tables. The listed events are those that are either i) worse in children than in adults (greater frequency rates compared to studies in adults of the same disorder, or greater difference from placebo rates, or greater severity), or ii) identified only in pediatric populations, and for which drug rates are greater than placebo.

TABLE 5: Adverse Events Reported in 2% or More of Subjects in One of the SAPHRIS® Dose Groups during short-term (3 weeks) treatment of children and adolescents with Bipolar I Disorder (ages 10-17 years), that were identified as worse in children compared to adults or unique to children, and greater than placebo.

	Pediatrics			
	Placebo (n=101)	Asenapine 2.5mg (n=104)	Asenapine 5.0mg (n=99)	Asenapine 10mg (n=99)
Nervous System Disorders				
Somnolence	5.9%	32.7%	34.3%	31.3%
Sedation	5.0%	15.4%	19.2%	18.2%
Headache	5.9%	7.7%	11.1%	9.1%
Dysgeusia	2.0%	3.8%	5.1%	9.1%
Parkinsonism	0	1.0%	0	2.0%
Psychiatric Disorders				
Suicidal Ideation	1.0%	3.8%	1.0%	3.0%
Anger	0	0	0	2.0%
Gastrointestinal Disorders				
Hypoaesthesia oral	2.0%	17.3%	18.2%	20.2%
Paraesthesia oral	2.0%	8.7%	9.1%	11.1%
Nausea	3.0%	5.8%	6.1%	6.1%
Abdominal Pain	0	2.9%	1.0%	1.0%
Abdominal Discomfort	0	1.0%	0	2.0%
Glossodynia	0	0	2.0%	0
Metabolism and Nutrition Disorders				
Increased appetite	2.0%	9.6%	9.1%	6.1%
Dehydration	1.0%	0	2.0%	0
General Disorders				
Fatigue	5.0%	3.8%	8.1%	13.1%
Irritability	1.0%	1.0%	1.0%	2.0%
Investigations				
Weight Increased	0.0%	5.8%	2.0%	2.0%
Blood Insulin Increased	0	0	2.0%	1.0%
ALT Increased	0	0	0	2.0%
AST Increased	0	0	0	2.0%
Respiratory, Thoracic and mediastinal disorders				

	Pediatrics			
	Placebo (n=101)	Asenapine 2.5mg (n=104)	Asenapine 5.0mg (n=99)	Asenapine 10mg (n=99)
Oropharyngeal pain	2.0%	0	3.0%	1.0%
Nasal congestion	1.0%	0	2.0%	0
Dyspnea	0	0	2.0%	0
Injury, Poisoning and procedural complications				
Muscle strain	0	0	0	2.0%
Cardiac Disorders	1.0%	2.9%	1.0%	0
Tachycardia	0	2.9%	0	0
Skin Disorders				
Rash	1.0%	0	1.0%	2.0%
Musculoskeletal Disorders				
Myalgia	0	0	2.0%	1.0%
Immune system disorders				
Seasonal allergy	0	0	1.0%	2.0%

TABLE 6: Adverse Events Reported in 2% or More of Subjects in One of the SAPHRIS Dose Groups during short-term (8 weeks) treatment of children and adolescents with Schizophrenia (ages 12-17 years), that were identified as worse in children compared to adults or unique to children, and greater than placebo.

	Pediatrics		
	Placebo (n=102)	Asenapine 2.5mg (n=98)	Asenapine 5.0mg (n=106)
Nervous Systems Disorder			
Somnolence	6.9%	20.4%	17.0%
Sedation	2.0%	4.1%	11.3%
Dizziness	1.0%	7.1%	1.9%
Headache	5.9%	7.1%	7.5%
Parkinsonism	0	1.0%	3.8%
Tremor	2.9%	0	4.7%
Psychiatric Disorders			
Insomnia	5.9%	5.1%	9.4%
Sleep Disorder	0	3.1%	0.9%
Anxiety	2.9%	2.0%	3.8%
Suicidal Ideation	0	2.0%	1.9%
Gastrointestinal Disorders			
Paraesthesia oral	0	3.0%	2.9%
Abdominal pain upper	2.0%	0	2.8%
General Disorders			
Asthenia	0	2.0%	0.9%
Pyrexia	2.0%	3.1%	1.9%
Infections			
Nasopharyngitis	2.0%	4.1%	2.8%
Influenza	0	0	2.8%
Investigations			

Weight Increased	1.0%	4.1%	2.8%
Acne	0	2.0%	0
Cardiac Disorders	1.0%	0	3.8%
Ear & Labyrinth Disorders	0	0	2.8%

Weight Gain in Children and Adolescents

Although not indicated for treatment of pediatric patients, asenapine was associated with greater effects on weight gain in these patients than in adults.

In a short term trial of pediatric bipolar I disorder patients, the mean change from baseline to endpoint in weight for placebo and asenapine 2.5 mg, 5 mg, and 10 mg twice daily, was 0.48, 1.72, 1.62, and 1.44 kg, respectively. The proportion of subjects with clinically significant weight gain ($\geq 7\%$ weight gain from baseline at endpoint) was 12.0 % for asenapine 2.5 mg twice daily, 8.9 % for asenapine 5 mg twice daily, and 8.0 % for asenapine 10 mg twice daily, compared to 1.1 % for placebo. In the long-term, open-label extension trial (50 weeks), a total of 34.8% of subjects experienced clinically significant weight increase (i.e., $\geq 7\%$ increase in body weight at endpoint). Overall mean (SD) weight gain at study endpoint was 3.5 (5.76) kg.

In a short term trial of pediatric schizophrenia patients, there was a statistically significant higher incidence of patients with $\geq 7\%$ weight gain (from baseline to endpoint) compared to placebo (3.1 %) for asenapine 2.5 mg twice daily (9.5 %) and asenapine 5 mg twice daily (13.1 %).

Metabolic Syndrome in Children and Adolescent Population:

Based on the criteria defined per the International Diabetes Federation (IDF), new onset metabolic syndrome was identified if subjects who did not meet IDF criteria for metabolic

syndrome at baseline met 3/5 criteria including obesity at any visit during treatment or endpoint. There were a greater number of subjects who met criteria for new onset metabolic syndrome (MBS) in the asenapine treatment groups in the short-term pediatric trials compared to placebo. There were more subjects in the bipolar study (0 subjects in placebo, 4 (3.8%) subjects in 2.5 mg BID asenapine, 5 (5.1%) subjects in 5.0 mg BID asenapine treatment group, and 2 (2.0%) subjects in 10.0 mg BID asenapine) than in the schizophrenia study (0 subjects in placebo, 1 (1%) subject in 2.5 mg BID asenapine, and 2 (1.9%) subjects in 5.0 mg BID asenapine treatment group) who met criteria for new-onset MBS despite shorter trial duration.

Extrapyramidal Symptoms (EPS) in Children and Adolescent Population:

In a short term trial of pediatric schizophrenia patients, 10.4% of the patients treated with 5.0 mg asenapine BID had at least one EPS related adverse reaction, compared to 5.1% of the patients treated with 2.5 mg asenapine BID and 3.9% for placebo. Akathisia, parkinsonism, and dystonia were the reactions that occurred more often in the asenapine treatment groups than placebo and with a dose dependent frequency. Only akathisia occurred in >5% in a single asenapine treatment group (5 mg BID).

In a short term trial of pediatric bipolar I disorder patients, EPS related adverse reactions were reported by 2.0% of placebo-treated patients, 3.8% of patients treated with 2.5 mg asenapine BID, 4% of patients treated with 5.0 mg asenapine BID, and 5.1% of patients treated with 10 mg asenapine BID. The most frequent reactions in the asenapine treatment groups were akathisia (0% for placebo, 1.9% for asenapine 2.5 mg BID, 2.0% for asenapine 5.0 mg BID, and 1.0% for asenapine 10 mg BID) and Parkinson-like events (0% for placebo, 1.0% for asenapine 2.5 mg BID, 0% for asenapine 5.0 mg BID and 4.0% for asenapine 10.0 mg BID).

Suicidal ideation and behaviour in Children and Adolescent Population:

The number of subjects with events of suicidal ideation was higher in a study of pediatric bipolar patients (5% of patients treated with placebo, 4.8% of patients treated with 2.5 mg asenapine BID, 6.1% of patients treated with 5.0 mg asenapine BID and 8.1% of patients treated with 10 mg asenapine BID) than in a study of pediatric schizophrenia patients (2.0% of patients treated with placebo, 5.1% of patients treated with 2.5 mg asenapine BID, and 2.8% of patients treated with 5.0 mg asenapine BID).

Dystonia In Children and Adolescent Population:

Although not indicated in patients <18 years of age, in a small pharmacokinetic study, pediatric patients aged 10-17 years appeared to be more sensitive to dystonia when a gradual up-titration schedule was not followed. The incidence of dystonia in paediatric clinical trials using a gradual up-titration was similar to that seen in adult trials.

Other Adverse Events Observed During the Pre-marketing Evaluation of Oral Asenapine

Following is a list of MedDRA terms that reflect treatment-emergent adverse events, as defined in the introduction of the ADVERSE REACTIONS section, reported by patients treated with SAPHRIS® at fixed or flexible doses of 5 or 10 mg twice daily during phase 2/3 trials, within a database of 3400 patients. All events assessed as possible adverse drug reactions have been included. In addition, medically/clinically meaningful events particularly those that are likely to be useful to the prescriber or that have pharmacologic plausibility, have been included. Events already listed in Table 1, 2, 3 and 4 or other parts of the ADVERSE REACTIONS section have

been excluded. Although the events reported occurred during treatment with SAPHRIS[®], they were not necessarily caused by it.

Events are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions:

frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in less than 1/100 but at least 1/1,000 patients; rare events are those occurring in less than 1/1,000.

Blood and lymphatic disorders:

Infrequent: anemia

Rare: thrombocytopenia

Cardiac disorders:

Infrequent: tachycardia, temporary bundle branch block

Eye disorders:

Infrequent: accommodation disorder

Gastrointestinal disorders:

Infrequent: oral paresthesia, glossodynia, swollen tongue, dysphagia

General disorders:

Rare: idiosyncratic drug reaction

Investigations:

Rare: hyponatremia

Nervous system disorders:

Infrequent: dysarthria, neuroleptic malignant syndrome, seizures, syncope, tardive dyskinesia

Abnormal Hematologic and Clinical Chemistry Findings

Comparisons between SAPHRIS[®] and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory parameters (lipids, fasting glucose, transaminases) revealed no medically important differences.

Glucose: (see also WARNINGS AND PRECAUTIONS, Hyperglycemia and Diabetes Mellitus): The proportion of patients with fasting glucose elevations ≥ 7.0 mmol/L at any point in the short-term trials: 14% for SAPHRIS[®]-treated patients vs 8% for placebo-treated patients in 6 week schizophrenia trials and 5% vs 2% respectively in 3 week bipolar trials.

Lipids (Triglycerides and Cholesterol): In 6 week schizophrenia trials, the proportion of patients with elevations of total cholesterol ≥ 6.2 mmol/L at any point was 17% for SAPHRIS[®]-treated patients versus 14% for placebo-treated patients. The proportion of patients with elevations in fasting triglycerides ≥ 2.26 mg/dL at any point was 22% for SAPHRIS[®] treated patients versus 13% for placebo-treated patients. In 3 week bipolar mania trials, the proportion of

patients with elevations in triglycerides ≥ 2.26 mmol/L at any point was 16% for SAPHRIS[®]-treated patients versus 12% for placebo-treated patients.

Hepatic enzymes: Transient, asymptomatic elevations of hepatic transaminases, alanine transferase (ALT), aspartate transferase (AST) have been seen commonly, especially in early treatment. In short-term placebo-controlled schizophrenia trials, there was a mean increase in transaminase levels for SAPHRIS[®]-treated patients of 1.6 units/L compared to a decrease of 0.4 units/L for placebo-treated patients. In short term, placebo-controlled bipolar mania trials, the mean increase in transaminase levels for SAPHRIS[®] treated patients was 8.9 units/L compared to a decrease of 4.9 units/L in placebo-treated patients. The proportion of patients with transaminase elevations ≥ 3 times upper limit of normal (ULN) at any point was 2.5% for SAPHRIS[®]-treated patients versus 0.6% for placebo-treated patients.

In a 3 week fixed-dose placebo-controlled bipolar mania trial, the proportion of patients with transaminase elevations ≥ 3 times upper limit of normal (ULN) at any point was 5% for 10 mg BID, 1% for 5 mg BID and 3% for placebo.

Prolactin (see also WARNINGS & PRECAUTIONS, Hyperprolactinemia): In 6-week placebo-controlled schizophrenia trials, there was a mean decrease in prolactin levels of 6.5 $\mu\text{g/L}$ for SAPHRIS[®]-treated patients compared to a decrease of 10.7 $\mu\text{g/L}$ for placebo-treated patients.. The proportion of patients with prolactin elevations ≥ 4 times ULN (at any point) were 5 % for SAPHRIS[®]-treated patients versus 1 % for placebo-treated patients. In 3-week placebo-controlled bipolar mania trials, there was a mean increase in prolactin levels of 4.9 $\mu\text{g/L}$ for SAPHRIS[®]-treated patients compared to a mean decrease of 0.2 $\mu\text{g/L}$ for placebo-treated patients. The proportion of patients with prolactin elevations ≥ 4 times ULN (at any point) were 2 % for SAPHRIS[®] treated patients versus 1 % for placebo-treated patients.

Creatine Kinase (CK): The proportion of adult patients with CK elevations >3 times ULN at any time were 6.4% and 11.1% for patients treated with SAPHRIS[®] 5 mg twice daily and 10 mg twice daily, respectively, as compared to 6.7% for placebo-treated patients in short-term, fixed-dose trials in schizophrenia and bipolar mania. The clinical relevance of this finding is unknown.

Post-Market Adverse Drug Reactions

The following adverse events have been reported since market introduction of SAPHRIS[®]. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with asenapine, including rare ($\geq 1/10,000 < 1/1000$) anaphylactic/anaphylactoid reactions, such as swollen tongue, angioedema and swollen throat (pharyngeal edema) (see WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions). For the majority of cases of anaphylaxis a relationship to asenapine could not be excluded.

There have been infrequent ($\geq 1/1000 < 1/100$) postmarketing reports of oral mucosal lesions in patients treated with asenapine, including ulcerations, blistering and inflammation. The majority of cases occurred within 2 weeks of initiating asenapine treatment.

In clinical trial and/or post-marketing experience, events of leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including SAPHRIS[®]. Granulocytopenia and agranulocytosis have also been reported with antipsychotic agents. (see WARNINGS AND PRECAUTIONS - Hematologic).

Rare cases of priapism have been reported with antipsychotic use, such as with SAPHRIS[®].

Salivary hypersecretion and anxiety have been reported in post-marketing use.

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

Atypical antipsychotic drugs, such as asenapine, have been associated with cases of sleep apnea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnea, SAPHRIS should be prescribed with caution.

Risks of somnambulism (sleep walking) and sleep-related eating disorder have been associated with the use of atypical antipsychotics including asenapine.

DRUG INTERACTIONS

Drug-Drug Interactions

Given the primary CNS effects of antipsychotics, caution should be used when SAPHRIS[®] is taken in combination with other centrally acting drugs (see DRUG INTERACTIONS, Drug-Lifestyle Interactions).

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 (see table below). With the exception of fluvoxamine (strong CYP1A2 inhibitor), none of the drugs resulted in clinically relevant alterations in asenapine pharmacokinetics.

TABLE 7. Summary of Effect of Coadministered Drugs on Exposure to Asenapine in Healthy Volunteers

Coadministered drug (Postulated effect on CYP450/UGT)	Dose schedules		Effect on asenapine pharmacokinetics		Clinical comment
	Coadministered drug	Asenapine	C _{max}	AUC _{0-∞}	
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 asenapine dose adjustment required

					<i>[see also Potential for SAPHRIS[®] to affect other drugs]</i>
Imipramine (CYP1A2/2C19/3A4 inhibitor)	75 mg Single Dose	5 mg single dose	+17%	+10%	No asenapine dose adjustment required
Cimetidine (CYP3A4/2D6/1A2 inhibitor)	800 mg twice daily for 8 days	5 mg single dose	-13%	+1%	No asenapine dose adjustment required
Carbamazepine (CYP3A4/1A2 inducer)	200 mg twice daily for 4 days 400 mg twice daily for 15 days	5 mg single dose	-16%	-16%	No asenapine dose adjustment required
Valproate (UGT1A4 inhibitor)	500 mg twice daily for 9 days	5 mg single dose	2%	-1%	No asenapine dose 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 drugs

Because of its α 1-adrenergic antagonism with potential for inducing orthostatic hypotension (see WARNINGS AND PRECAUTIONS), SAPHRIS[®] may enhance the effects of certain antihypertensive agents.

In vitro studies indicate that asenapine weakly inhibits CYP2D6. Following co-administration of dextromethorphan and asenapine in healthy subjects, the ratio of dextromethorphan (a metabolite of dextromethorphan) and 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 2.5-fold decrease in DX/DM ratio. In the same study, treatment with paroxetine 20 mg daily produced a more pronounced, 30-fold decrease in the DX/DM ratio. 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, SAPHRIS[®] should be co-administered cautiously with drugs that are both substrates and inhibitors for CYP2D6.

Drug-Food Interactions

Eating and drinking should be avoided for 10 minutes after administration (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

A crossover study in 26 healthy male subjects was performed to evaluate the effect of food on the pharmacokinetics of a single 5 mg dose of asenapine. Consumption of food immediately prior to sublingual administration decreased asenapine exposure by 20%; consumption of food 4 hours after sublingual administration decreased asenapine exposure by about 10%. These effects are probably due to increased hepatic blood flow.

In clinical trials establishing the efficacy and safety of SAPHRIS[®], patients were instructed to avoid eating for 10 minutes following sublingual dosing. There were no other restrictions with regard to the timing of meals in these trials (see DOSAGE AND ADMINISTRATION).

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been studied.

Drug-Lifestyle Interactions

Alcohol/CNS Drugs: Given the primary CNS effects of asenapine, as with most psychoactive medications, use of asenapine with alcohol or other CNS drugs with overlapping undesirable effects such as sedation, should be avoided.

Smoking: A population pharmacokinetic analysis indicated that smoking, which induces CYP1A2, had no effect on the clearance of asenapine in smokers. In a crossover study in which 24 healthy male subjects (who were smokers) were administered a single 5 mg sublingual dose, concomitant smoking had no effect on the pharmacokinetics of asenapine.

DOSAGE AND ADMINISTRATION

General Considerations

SAPHRIS[®] is a sublingual tablet. To ensure optimal absorption, patients should be instructed to place the tablet under the tongue and allow it to dissolve completely. The tablet will dissolve in saliva within seconds. SAPHRIS[®] sublingual tablets should not be crushed, chewed, or swallowed. To allow sublingual absorption, patients should be instructed to **not eat or drink for 10 minutes after administration of SAPHRIS[®]**.

Recommended Dose and Dosage Adjustment

Schizophrenia

The recommended starting and target dose of SAPHRIS[®] is 5 mg given twice daily. In short term controlled trials, there was no suggestion of added benefit with a 10 mg twice daily dose, but there was a clear increase in certain adverse reactions (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Dose-Related Adverse Drug Reactions). The safety of doses above 10 mg twice daily has not been evaluated in clinical studies in schizophrenia.

Bipolar Disorder

The recommended starting dose of SAPHRIS[®] is 5 mg twice daily. The dose can be increased to 10 mg twice daily, based on individual clinical response and tolerability.

In a short-term, fixed-dose controlled monotherapy trial there was no evidence of added benefit with a 10 mg twice daily dose compared to 5 mg twice daily.

In a trial of SAPHRIS[®] administered concurrently with valproate or lithium, the starting dose of SAPHRIS[®] was 5 mg twice daily. On subsequent days the dose could be increased to 10 mg twice daily. Fifty-five percent of patients remained on 5 mg twice daily throughout the trial while 45% of patients had a dosage increase to 10 mg twice daily at some time point during the trial.

The safety of doses above 10 mg twice daily has not been evaluated in clinical trials in bipolar disorder.

Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia or bipolar mania from other antipsychotics to SAPHRIS[®] or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

Dosing Considerations in Special Populations

- Elderly patients - No dosage adjustment needed.
- Patients with renal impairment - No dosage adjustment needed.
- Patients with mild and moderate hepatic impairment - No dosage adjustment needed.
- Severe hepatic impairment - SAPHRIS[®] is not recommended.

Missed Dose

If a tablet is missed at its usual time, it should be taken as soon as possible. But, if it is too close to the time of the next dose, only the prescribed dose should be taken at the appointed time. **A double dose should not be taken.**

Administration

SAPHRIS[®] is a sublingual tablet. **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 blister pack. The coloured tab should be peeled back and the tablet should be removed gently. The tablet should not be crushed. If other medications are being taken by mouth concomitantly, SAPHRIS[®] should be taken last.

OVERDOSAGE

For management of suspected drug overdose, contact the regional Poison Control Centre.
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Few cases of overdose were reported in the asenapine program. Among these few reported cases of overdose, the highest estimated ingestion of SAPHRIS[®] was 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).

Management of Overdosage

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 (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 up-to-date information on the management of a suspected drug overdose, contact the regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

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 D₂ and 5-HT_{2A} receptors. Actions at other receptors e.g., 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-HT₆, 5-HT₇, D₃, and α ₂-adrenergic receptors, may also contribute to the clinical effects of asenapine.

Pharmacodynamics

Asenapine exhibits high affinity for serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT₅, 5-HT₆, and 5-HT₇ receptors (K_i values of 2.5, 2.7, 0.07, 0.18, 0.03, 1.6, 0.25, and 0.11 nM, respectively), dopamine D_{2A}, D_{2B}, D₃, D₄, and D₁ receptors (K_i values of 1.3, 1.4, 0.42, 1.1, and 1.4 nM, respectively), α _{1A}, α _{2A}, α _{2B} and α _{2C}-adrenergic receptors (K_i values of 1.2, 1.2, 0.33, and 1.2 nM, respectively), and histamine H₁ receptors (K_i value 1.0 nM), and moderate affinity for H₂ receptors (K_i value of 6.2 nM). In *in vitro* assays asenapine acts as an antagonist at these receptors, with the possible exception of some partial agonistic activity on the 5-HT_{1A} receptor. Asenapine has no appreciable affinity for muscarinic cholinergic receptors (e.g., K_i value of 8128 nM for M₁).

Pharmacokinetics

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 estimated at 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 less than proportional increase of C_{max} and AUC with dose may be attributed to limitations in the absorption capacity from the oral mucosa following sublingual administration. 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 asenapine exposure of 19% and 10%, respectively. Therefore, eating and drinking should be avoided for 10 minutes after administration (see DOSAGE AND ADMINISTRATION).

Distribution: Asenapine is rapidly distributed and has a large volume of distribution (approximately 20 - 25 L/kg), indicating extensive extravascular distribution. Asenapine is highly bound (95%) to plasma proteins, including albumin and α 1-acid glycoprotein.

Metabolism and Excretion: Direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2) are the primary metabolic pathways for asenapine.

Asenapine is a high clearance drug with a clearance after intravenous administration of 52 L/h. In this circumstance, hepatic clearance is influenced primarily by changes in liver blood flow rather than by changes in the intrinsic clearance, i.e., the metabolizing enzymatic activity. Following an initial more rapid distribution phase, the terminal half life of asenapine is approximately 24 hours. Data from clinical positron emission tomography (PET) studies indicate that twice daily dosing is required to maintain a sufficient level of receptor occupancy. 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.

After administration of a single dose of [¹⁴C]-labeled asenapine, about 90% of the dose was recovered; approximately 50% was recovered in urine, and 40% recovered in feces. About 50% of the circulating species in plasma have been identified. The predominant species was asenapine N⁺-glucuronide; others included N-desmethyiasenapine, N-desmethyiasenapine N-carbamoyl glucuronide, and unchanged asenapine in smaller amounts. SAPHRIS[®] (asenapine) sublingual tablet activity is primarily due to the parent drug.

In vitro studies indicate that asenapine is a substrate for UGT1A4, CYP1A2 and to a lesser extent CYP3A4 and CYP2D6. Asenapine is a weak inhibitor of CYP2D6. Asenapine does not cause induction of CYP1A2 or CYP3A4 activities 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 DRUG INTERACTIONS).

Special Populations and Conditions

Pediatrics (10-17 years of age): SAPHRIS[®] is not indicated for use in patients <18 years of age. Overall, exposure to asenapine at the same dose level appeared to be similar between the pediatric population (10-17 years) and adults (\geq 18 years) with the concentration-time profiles largely comparable and overlapping. 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. In a small PK study, exposure to N-desmethyiasenapine at 10 mg BID, was higher (~2-fold) in the age group of 10-11 years (n=4) compared to the other groups.

Geriatrics: In elderly patients (n=96) with psychosis (65-85 years of age), exposure to asenapine is approximately 30 % higher compared to younger adult patients. No dose adjustment is necessary.

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 clinically relevant effects of race on the pharmacokinetics of asenapine were found.

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.

Renal Insufficiency: 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.

STORAGE AND STABILITY

Store at 2° C to 30° C. Store in the original package. **The tablet should not be removed from the blister until ready to take it.**

Keep out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each SAPHRIS® (asenapine) sublingual tablet contains 5 mg or 10 mg asenapine (as maleate).
Non-medicinal ingredients: gelatin, mannitol.

5 mg

Round, white to off-white, fast dissolving, sublingual tablets debossed with “5” on one side.
Peelable aluminium blister strips in cartons of 60 sublingual tablets per carton.

10 mg

Round, white to off-white, fast dissolving, sublingual tablets debossed with “10” on one side.
Peelable aluminium blister strips in cartons of 60 sublingual tablets per carton.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: asenapine maleate

Chemical name:

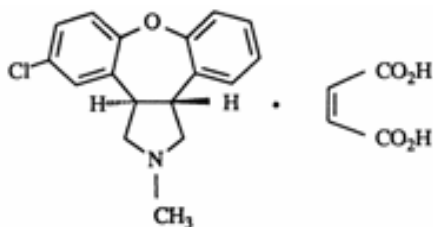
(3aR,12bR)-rel-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole (2Z)-2-butenedioate (1:1) (CA Index Name)

trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole (Z)-2-butenedioate (1:1)

Molecular formula: C₁₇H₁₆ClNO.C₄H₄O₄

Molecular mass: 401.84

Structural formula:



Physicochemical properties: Asenapine maleate is white to off-white powder. The solubility in water is 5.2 mg/mL asenapine maleate. The melting point has an average onset temperature of 139.9°C. The logarithm of the n-octanol/water coefficient (log P_{ow}) is 4.9 (neutral species) and 1.4 (cationic species) at 21.5-23.8°C. The pK_a value of the protonated free base of asenapine maleate is 8.6 at 21.5-23.8°C.

pH in solution:

Asenapine maleate 0.1% m/v solution in water, 23.5°C: 4.6

Asenapine maleate saturated solution in water, 23.5°C: 4.2

Specific optical rotation:

[α]_D^{20°C} (10 mg/mL in methanol): -0.2°

[α]_D^{25°C} (10 mg/mL in methanol): 0.0°

CLINICAL TRIALS

Clinical Efficacy in Schizophrenia

Short-Term Trials (6-week)

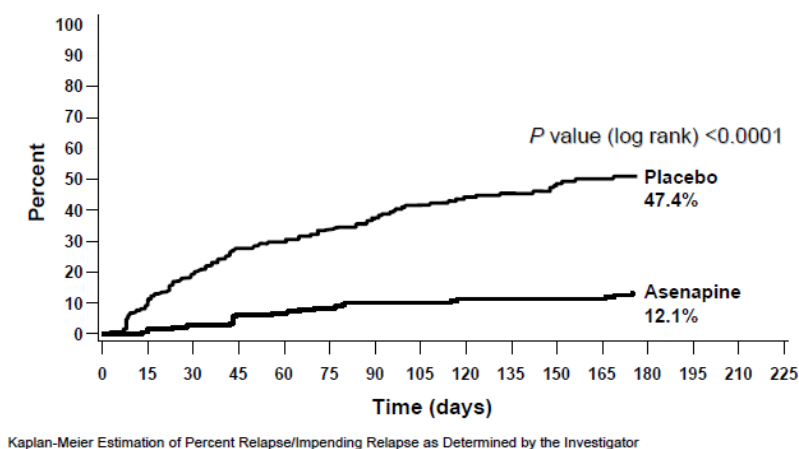
The efficacy of SAPHRIS[®] in the treatment of schizophrenia was evaluated in three fixed-dose and one flexible dose, short-term (6 weeks), randomized, double-blind, placebo and active-controlled trials of patients who met DSM IV criteria for schizophrenia and were having an acute exacerbation of their schizophrenic illness. All four trials included an active control group (risperidone, olanzapine, or haloperidol) but were not designed to compare SAPHRIS[®] with the active comparator. The primary efficacy rating scale was the Positive and Negative Syndrome Scale (PANSS). The primary and secondary efficacy endpoints included change from baseline on PANSS total score and each of the PANSS subscale scores (PANSS positive, negative and general psychopathology subscales), the PANSS Marder factor scores and the Clinical Global Impression severity score (CGI-S).

In two of the trials (041004 & 041023), SAPHRIS[®] demonstrated superior efficacy to placebo. In the third trial, 041021, SAPHRIS[®] could not be distinguished from placebo, however, an active control in that trial was superior to placebo. In the fourth trial (041022) neither SAPHRIS[®] nor the active control in the trial were superior to placebo.

Longer-Term Trial (A7501012: open label (26-week) & double-blind randomized withdrawal (26-week))

A total of 700 patients entered the open-label treatment with SAPHRIS[®] for up to 26 weeks (5 or 10 mg twice daily; flexible dosing). Of these, a total of 386 patients met criteria for stabilization on SAPHRIS[®] and were randomized double blind to ongoing treatment with SAPHRIS[®] or to placebo for up to 26 weeks. SAPHRIS[®] was statistically significantly more effective than placebo in prolonging the time to relapse or impending relapse (i.e. symptom exacerbation defined by protocol specified threshold scores or change scores on PANSS and CGI or increased interventions) on Kaplan-Meier curves. At the 26-week endpoint, 47 percent of the placebo-treated patients relapsed*, compared with only 12 percent of the SAPHRIS[®]-treated patients (p<0.0001).

Figure 1: Time to Relapse* in Trial A7501012



*Relapse/impending relapse during the double-blind phase was defined as a) CGI-S score of ≥ 4 (moderately ill) on at least 2 days within 1-week period and increase of $\geq 20\%$ in PANSS total score, or scores of ≥ 5 (moderately severe) on the hostility or uncooperativeness items of the PANSS, or scores of ≥ 5 (moderately severe) on the unusual thought content, conceptual disorganization or hallucinatory behavior items of the PANSS; b) increase in the level of psychiatric care and use of rescue medications due to worsening of schizophrenia.

Clinical Efficacy in Bipolar I Disorder

Short-Term Trials (3-week)

The efficacy of SAPHRIS[®] monotherapy in the treatment of acute mania was studied in three similarly designed 3-week, randomized, double-blind, placebo-controlled trials, involving adult patients who met DSM-IV criteria for Bipolar I Disorder, with an acute manic or mixed episode, with or without psychotic features. Two of the studies were flexible-dose, with an active-control olanzapine arm (A7501004 & A7501005), and one was a fixed-dose study (P05691)

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (YMRS).

In both flexible-dose trials, all 379 patients randomized to SAPHRIS[®] were initially administered 10 mg twice daily, and the dose could be adjusted within the range of 5 to 10 mg twice daily, from Day 2 onward based on efficacy and tolerability. Based upon per-protocol LOCF analysis, SAPHRIS[®] was superior to placebo on the YMRS total score (see Table 8) and the Clinical Global Impression–Bipolar Severity of Illness score (mania) from Day 2 onwards. SAPHRIS[®] demonstrated superior efficacy to placebo in the reduction of manic symptoms over 3 weeks.

In the fixed-dose trial, 126 patients received placebo, 122 received asenapine 5 mg twice daily (BID), and 119 received asenapine 10 mg BID. Based upon per-protocol MMRM analysis, both asenapine doses (5 mg BID and 10 mg BID) were superior to placebo in change from baseline in YMRS total score at Day 21 (see Table 8) A statistically significant difference between asenapine and placebo was seen as early as day 2. In this short-term, fixed-dose controlled trial

there was no evidence of added benefit with a 10 mg twice daily dose compared to 5 mg twice daily.

TABLE 8. 3-week Bipolar Mania Trials

Study Number	Treatment Group	Primary Efficacy Measure: YMRS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference ^a (95% CI)
Trials 1&2 (Flexible dose)	SAPHRIS 5-10 mg* twice daily	28.8 (6.2)	-11.1 (0.5)	-4.5 (-6.3, -2.7)
	Placebo	28.7 (6.3)	-6.7 (0.7)	--
Trial 3 (Fixed dose)	SAPHRIS 5 mg* twice daily	29.7 (5.9)	-14.4 (1.0)	-3.5 (-6.3, -0.7)
	SAPHRIS 10 mg* twice daily	30.2 (5.4)	-14.9 (1.0)	-4.0 (-6.9, -1.2)
	Placebo	30.0 (5.6)	-10.9 (1.0)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiple comparisons.

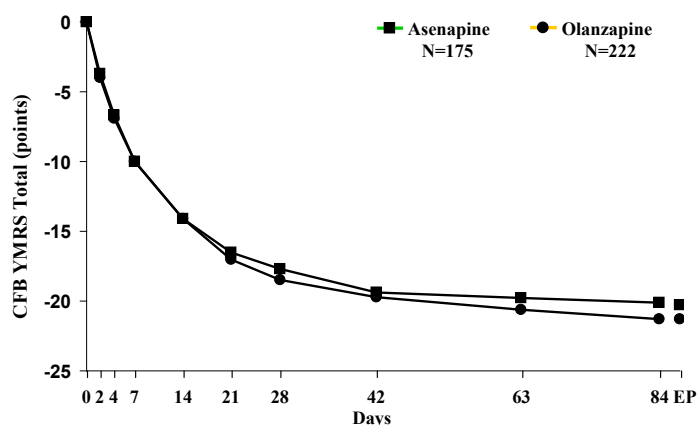
^a Difference (drug minus placebo) in least-squares mean change from baseline.

* Doses that are demonstrated to be effective.

9-Week Extension Trial

In addition, subjects who were on active treatment and completed trials A7501004/5 could continue on the same active treatment (SAPHRIS[®] 5-10 mg twice daily or olanzapine 5-20 mg once daily) in an extension trial (A7501006, n=397) for an additional 9 weeks. In this extension trial, maintenance of effect of SAPHRIS[®] during the additional 9 weeks was shown.

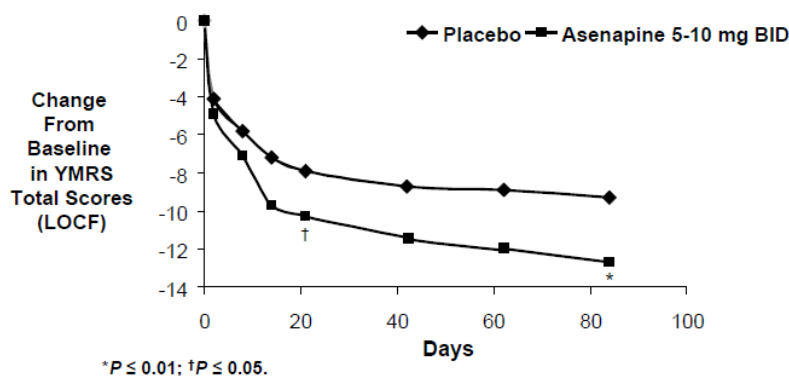
Figure 2: Change from baseline on YMRS Total Score Intent-to-Treat, LOCF, A7501006



Co-therapy Trial (12-week)

In a 12-week, randomized, placebo-controlled trial (A7501008) involving 318 patients with a manic or mixed episodes of Bipolar I Disorder, with or without psychotic features, who had been receiving lithium or valproate monotherapy for at least 2 weeks, prior to randomization, the addition of SAPHRIS[®] resulted in superior efficacy compared to lithium or valproate monotherapy at week 3 up to week 12 post-randomization in the reduction of manic symptoms.

Figure 3: Change from baseline in YMRS total score, LOCF (Trial A7501008)



DETAILED PHARMACOLOGY

Nonclinical Pharmacology

The pharmacodynamic properties of asenapine have been determined in a wide variety of *in vitro* and *in vivo* tests used for characterization of putative agents for the treatment of schizophrenia and bipolar disorder.

Asenapine is a multi-receptor antagonist with a different rank order of human receptor-binding affinities for serotonin, norepinephrine, dopamine, and histamine receptors when compared with risperidone, olanzapine, quetiapine, clozapine, aripiprazole, ziprasidone, and haloperidol. In comparison to other antipsychotics, asenapine has a strong interaction with a broader set of human 5-HT receptors, showing subnanomolar binding affinity (K_i) for (nM): 5-HT_{2C} (0.03), 5-HT_{2A} (0.07), 5-HT_{2B} (0.18), 5-HT₆ (0.25), and 5-HT₇ (0.11); α_{2B}-adrenergic receptors (0.33); and D₃ (0.4) receptors. Affinity at these receptors was higher than that for the D_{2A} (1.3 nM) and D_{2B} (1.4 nM) receptors. Asenapine has nanomolar level of affinity for (nM): 5-HT_{5A} (1.6), 5-HT_{1A}, (2.5), 5-HT_{1B} (2.7), α_{1A} (1.2), α_{2A} (1.2), α_{2C} (1.2), H₁ (1.0), H₂ (6.2), D₁ (1.4). Asenapine blocked agonist-induced activation of 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1B}, 5-HT₆, 5-HT₇, D₁, D₂, D₃, α_{1A}, α_{2A}, α_{2B}, α_{2C}, H₁, and H₂ receptors. In contrast to olanzapine, quetiapine, and clozapine, asenapine has no appreciable affinity for muscarinic receptors. Furthermore, asenapine also shows appreciable affinity for H₂ receptors. Asenapine (1 nM to 5 nM)

potentiated N-methyl D-aspartic acid (NMDA) receptor evoked current responses in rat cortical pyramidal cells, suggesting that it may also enhance glutamatergic activity through an indirect mechanism.

In vivo receptor occupancy analysis in rat brain showed that asenapine produced time- and exposure-related increases in D₂ and 5-HT_{2A} receptor occupancy. Plasma levels of 0.48 ng/mL and 1.24 ng/mL were necessary for 50% receptor occupancy at the 5-HT_{2A} and D₂ receptor, respectively. The range for plasma levels to achieve 60%-80% D₂ receptor occupancy, thought to be necessary for antipsychotic activity, was 1-3 ng/mL.

Asenapine acts as a potent antagonist at 5-HT_{2A}, α_2 -adrenergic, and D₂ receptors in rat brain. Electrophysiological experiments in anesthetized rats showed that asenapine potently blocked the inhibitory effects of 5-HT_{2A} (ED₅₀: 0.075 mg/kg, IV) and α_2 adrenergic (ED₅₀: 0.085 mg/kg, IV) receptor activation on noradrenergic locus coeruleus neurone firing. D₂ receptor evoked inhibition of dopaminergic, ventral tegmental, neurone activity was also blocked by asenapine (ED₅₀: 0.040 mg/kg, IV). Chronic administration of asenapine (0.03, 0.1, 0.3 mg/kg, SC, twice daily) exerted dose-dependent and regionally specific effects on serotonin, α -adrenergic, dopamine and inotropic glutamate receptor subtypes. In general, its effects were similar to that observed with atypical antipsychotic drugs. Thus, it increased D₂-receptor binding and decreased 5-HT_{2A} binding density in rat brain in a regionally specific manner. Increases in α_1 and α_2 adrenoceptor, as well 5HT_{1A} receptor-binding density in prefrontal cortex, were also observed with asenapine. These changes in monoamine receptor-binding density are likely to be due to an adaptive response to long-term blocking action by asenapine at serotonin, dopamine, and noradrenergic receptors. In parallel to changes in dopamine, serotonin, and α -adrenergic receptors, chronic administration of asenapine was also associated with alterations in glutamate NMDA and 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propionic acid (AMPA) receptor binding density. Overall, the receptor pharmacology data show that asenapine shares some key characteristics with atypical antipsychotics, such as strong affinity and blockade of the D₂ receptor, combined with α_2 -adrenergic receptor antagonism, and relatively higher affinity, for the 5-HT_{2A} receptor.

Asenapine (0.001 to 3 mg/kg, SC) in acute rodent behavioral studies demonstrated potent anti-serotonergic and anti-dopaminergic properties as well as activity in tests predictive of antipsychotic efficacy. Asenapine (0.05, 0.1, 0.2 mg/kg SC) produced a dose-related suppression of conditioned avoidance response with an ED₅₀ of 0.12 mg/kg. It showed preferential inhibition of locomotor activity stimulated by low doses of amphetamine (1 mg/kg SC) versus locomotor activity stimulated by high doses of amphetamine (3 mg/kg SC), with asenapine (minimal effective doses [MEDs] of 0.03 and 0.1 mg/kg (SC), respectively. Asenapine MED: 0.03 mg/kg SC), reversed apomorphine-induced disruption of prepulse inhibition in rats. In rat or monkey behavioural models of cognitive dysfunction, asenapine (0.05 - 0.15 mg/kg SC) was able to improve performance in tasks examining cognitive flexibility or reversal learning. Asenapine (0.06 to 0.6 mg/kg, twice daily, IP) treatment, over a 5-week period, reduced chronic mild stress-induced loss of sucrose intake (putative model of anhedonia) in rats.

At doses consistent with antipsychotic and other behavioral activity, asenapine (0.05-0.5 mg/kg, SC) increased dopamine efflux in rat mPFC, hippocampus, nucleus accumbens, and striatum. It also elevated norepinephrine and acetylcholine efflux in mPFC and hippocampus across a similar dose range. Furthermore, at 0.2 mg/kg (SC), asenapine produced increases in 3,4-

dihydroxyphenylacetic acid (DOPAC) levels in rat medial prefrontal cortex (mPFC), nucleus accumbens, and striatum as well as in 5-hydroxyindoleacetic acid (5-HIAA) levels in mPFC and nucleus accumbens, indicating that it stimulates 5-HT and dopamine metabolism in the mPFC and nucleus accumbens following acute administration.

In the catalepsy test (predictive of EPS liability) in rats, relatively higher doses (MED: 1 mg/kg SC) of asenapine were needed to produce a cataleptic effect. This is consistent with the profile of other atypical antipsychotic drugs showing a relatively higher affinity for the 5-HT_{2A} receptor over the D₂ receptor a property which has been suggested to be indicative of low potential for induction of EPS.

Enantiomer and Metabolite Pharmacology

The nonclinical pharmacology of the two enantiomers of asenapine suggests that both are involved in mediating the pharmacodynamic effects of asenapine. This is based on both *in vitro* and *in vivo* data suggesting that the two enantiomers do not differ appreciably from the pharmacological profile of asenapine. Contribution of pharmacological activity from the metabolites of asenapine is considered to be unlikely at the therapeutic dose range of 5-10 mg twice daily. Pharmacological analysis has shown that the identified metabolites have much reduced (e.g. D₂ and 5-HT_{2A} receptor) activity, relatively low exposure and/or inability to cross the blood brain barrier.

Safety pharmacology

Specific studies were conducted with asenapine to evaluate effects on cardiac depolarization. When tested in the hERG assay, the extrapolated IC₂₀ for asenapine was 67-fold greater than its estimated efficacious free concentration in humans after 10 mg twice daily. Similarly, the N-desmethyl metabolite, is not expected to interact with the hERG channel at clinically relevant concentrations. The N⁺-glucuronide metabolite had no hERG activity.

The results of a study in isolated canine Purkinje fibers indicate that asenapine induced mainly decreases in action potential duration, in particular on APD₅₀. These effects were associated with a decrease in the plateau of action potential involving mainly calcium channel current. N-desmethyласenapine induced comparable effects, but at approximately 10 times higher concentrations.

In conscious rats, a subcutaneous single dose of 5 mg/kg asenapine induced a transient central respiratory depressor effect, 20 minutes after administration. The no effect level was 1.5 mg/kg with an estimated C_{max} of 100 ng/mL.

Safety pharmacology studies showed that asenapine induces cardiovascular effects (decrease in arterial blood pressure, tachycardia, and orthostatic hypotension), the two enantiomers being equally active. N-desmethyласenapine has a lower intrinsic activity both *in vivo* and *in vitro*.

Asenapine may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially early in treatment, probably reflecting its α₁-adrenergic antagonist properties.

Pharmacokinetics

The overall pharmacokinetic attributes of asenapine in laboratory animals are marked by a relatively high clearance, high volume of distribution, and short half-life. The pharmacokinetics were linear with dose (except for high oral doses), stationary with repeated dosing, and did not show significant gender differences. The pharmacokinetics of individual enantiomers were similar to each other in the dog and human, and some minor differences were observed in other species. Asenapine readily penetrates membranes (as demonstrated *in vitro*) which yields high absorption, facile penetration into the CNS, distribution into tissues (including the placental transfer) and secretion into milk. Binding to plasma proteins is relatively high with free fractions in laboratory animals ranging between 2 to 4%. Asenapine has some affinity to melanin-containing tissues (eye and skin).

Metabolism

Metabolism of asenapine occurs via oxidative and conjugative pathways. Metabolites observed were numerous and arose via multiple sequential pathways, yielding a complex metabolic profile. Human plasma metabolites included asenapine N⁺-glucuronide, N-desmethyiasenapine, and N-desmethyiasenapine-N-carbamoylglucuronide, among others, and the N-oxide metabolite was important in animals only. Metabolites observed in humans are also observed in laboratory animals at least on the basis of retention time comparison. In addition, all metabolic pathways as observed in human have been observed in preclinical species.

Excretion

Drug related material was excreted in both urine and feces; the percentages varied among the species. Unchanged asenapine accounted for 2 to 16% of total dose excreted, with the remainder being metabolites. *In vitro* studies on human enzymes involved in the metabolism of asenapine guided the design of clinical studies on the effect of CYP3A4 inhibition (cimetidine) and induction (carbamazepine), of CYP2D6 inhibition (paroxetine), of CYP2C19 inhibition (imipramine), of CYP1A2 inhibition (fluvoxamine) and of UGT inhibition (valproic acid). The effects on pharmacokinetics of asenapine and selected relevant metabolites are in line with the *in vitro* results and are shown to be of limited clinical importance. Only coadministration with fluvoxamine, a strong CYP1A2 inhibitor, can be expected to result in relevant increases in asenapine plasma concentrations. *In vivo*, asenapine has a weak inhibitory effect on CYP2D6, but may enhance the inhibitory effects drugs that are both substrates and inhibitors for CYP2D6, as shown with paroxetine, resulting in an increase in paroxetine exposure.

TOXICOLOGY

Acute toxicity

In rats the oral LD₅₀ values were in the range of 110 to 176 mg/kg. Male dogs tolerated up to 200 mg/kg as a single oral dose with CNS signs at ≥50 mg/kg. Intravenous administration of asenapine to rat caused no deaths up to the maximum achievable dose of 21 mg/kg. Important clinical signs were primarily of CNS nature and comprised convulsions, motor incoordination, reduced activity/ventral recumbency, and stereotypic behavior (dog).

Repeated-dose toxicity

Morbidity/mortality at high dose levels in repeat-dose toxicity studies were referable to effects on the CNS, including convulsions and attributable to exaggerated pharmacology. Mild clinical signs such as hypoactivity and miosis occurred in animals at low dose levels and associated systemic concentrations were less than at the human therapeutic level. 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. Liver microscopic changes were seen in some repeated dose rat studies, consisting mainly of hepatocellular hypertrophy that was considered due to microsomal enzyme induction that also resulted in increased liver weight and thyroid follicular cell hypertrophy. These findings are not likely to be relevant to patients, since hepatic enzyme induction in human hepatocytes only occurred at asenapine concentrations much higher than therapeutic levels. Adrenal weight increases and microscopic changes were present in rats. In animals, prolactin-mediated effects on reproductive organs and mammary gland in females occurred at sub-therapeutic systemic exposure levels.

During the drug withdrawal period (duration 6 weeks) in 1-year oral studies in rats and dogs evidence of (partial) recovery was observed. There were no indications of delayed effects attributable to dose discontinuation using standard toxicological endpoints.

Mutagenesis

No evidence for genotoxic potential of asenapine was found in the *in vitro* bacterial reverse mutation assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assays in human lymphocytes, the *in vitro* sister chromatid exchange assay in rabbit lymphocytes, or the *in vivo* micronucleus assay in rats.

Carcinogenicity

In a lifetime carcinogenicity study in CD-1 mice asenapine was administered subcutaneously at doses up to those resulting in plasma levels (AUC) estimated to be 5 times those in humans receiving the maximum recommended human dose (MRHD) of 10 mg twice daily. The incidence of malignant lymphomas was increased in female mice, with a no-effect dose resulting in plasma levels estimated to be 1.5 times those in humans receiving the MRHD. The mouse strain used has a high and variable incidence of malignant lymphomas, and the significance of these results to humans is unknown. There were no increases in other tumor types in female mice. In male mice, there were no increases in any tumor type.

In a lifetime carcinogenicity study in Sprague-Dawley rats, asenapine did not cause any increases in tumors when administered subcutaneously at doses up to those resulting in plasma levels (AUC) estimated to be 7.5 times those in humans receiving the MRHD.

Impairment of Fertility

Asenapine did not impair fertility in rats when tested at doses up to 10.6 mg/kg twice daily given orally. This dose is 10 times the maximum recommended human dose of 10 mg twice daily given sublingually on a mg/m² basis.

Reproductive and developmental toxicity

In reproduction toxicology studies using rabbits and rats, asenapine was embryotoxic. There was no evidence of teratogenicity in rat fertility and pre- and post-natal studies or embryo-fetal development studies in rabbits (oral and IV) or in rats dosed via the oral route. However an increased incidence of skeletal abnormalities was seen in rats given 1.5 mg/kg during gestation by the IV route, while 0.9 mg/kg was a NOEL with an associated AUC-based exposure margin of 3.4 compared to a 10 mg twice daily human therapeutic dose. Embryo-fetal toxicity, including delayed ossification and decreased fetal weight, was seen at 10.6 mg/kg twice daily given orally to rats and rabbits during gestation, while 1.8 mg/kg twice daily was a NOAEL in both species with associated margins, relative to a 10 mg twice daily human therapeutic dose, of 1.75 and 3 fold, respectively, on a mg/m² basis. In the rat fertility study, increased pre- and post implantation loss at 1.8 and 10.6 mg/kg twice daily and increased pup loss and delayed skeletal development occurred at all dose levels (0.35-10.8 mg/kg twice daily) and hence a NOAEL for embryo-fetal toxicity was not identified in this study. When asenapine was administered intravenously to pregnant rabbits at dose levels up to 0.44 mg/kg, no signs of embryotoxicity were observed and the resulting margin is 2.7 based on AUC comparison to humans taking 10 mg twice daily. Increased neonatal mortality was observed in all asenapine dose groups among the offspring of female rats treated during gestation and lactation at 0.3 – 1.5 mg/kg IV. From a cross-fostering study, it was concluded that asenapine induced peri- and postnatal losses were caused by an effect on the pups rather than altered nursing behaviour of the dams. A NOAEL was not identified at asenapine dose levels as low as 0.3 mg/kg IV which is associated with exposure slightly (30%) above human therapeutic levels.

Asenapine caused maternal toxicity at all dose levels or at sub-therapeutic exposures in all reproductive/developmental toxicity studies except the oral rabbit study.

Local tolerance

Local tolerance of asenapine sublingual tablets was tested in female dogs. Administration of up to 15 mg twice daily using sublingual tablets containing 5 mg asenapine for 7 consecutive days did not induce any macroscopical or histopathological changes at the site of treatment.

Other toxicity studies

Antigenicity

Asenapine administered either orally or subcutaneously (0.03 - 3 mg/kg) to the guinea-pig did not cause any sign of antigenicity as determined by active anaphylaxis, the passive cutaneous anaphylaxis test, and the delayed hypersensitivity test.

Phototoxicity

Since the UV spectrum of asenapine shows some residual absorption at wavelengths above 290 nm, it was tested in the *in vitro* 3T3 Neutral Red Uptake assay for phototoxicity. The results show that asenapine is not phototoxic in this model.

Prolactin release and locomotor activity

Asenapine was administered subcutaneously (2.8 mg/kg) to mature male Sprague Dawley rats for 28 days to study the pattern of locomotor activity during the recovery phase and to examine the effects on prolactin release after single dosing. Risperidone (5 mg/kg p.o) served as a comparator. Withdrawal of treatment was followed by a long period of increased daylight activity. After 8 weeks, the activity was no longer significantly different from Control. Risperidone did not show evidence of any increase in activity once treatment had stopped.

In a study with similar design, plasma prolactin was assessed after single and multiple dosing. The response of mature male Sprague Dawley rats to treatment with asenapine or risperidone was essentially similar, and the increases in prolactin release both after single or multiple dosing were similar in the treated groups.

Juvenile toxicity

Asenapine administration by the subcutaneous route to 2-week old juvenile rats for 8 weeks did not affect learning, memory, motor coordination or reproductive performance but increased locomotor activity after withdrawal of drug treatment at all dose levels, that showed signs of recovery in males, but not females, up to 30 days after cessation of dosing. Therefore a NOAEL was not identified.

REFERENCES

1. Bosveld-van Haandel LJM, Slooff CJ, van den Bosch RJ. Reasoning about the optimal duration of prophylactic antipsychotic medication in schizophrenia: evidence and arguments. *Acta Psychiatr Scand* 2001;103:335-46.
2. Bymaster FP, Calligaro DO, Falcone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology* 1996;14(2):87-96.
3. Freedman R. Schizophrenia. *N Engl J Med* 2003;349:1738-49.
4. Guy W. CGI: clinical global impressions. In: *ECDUE assessment manual for psychopharmacology, revised*. 1976, 217-222.
5. Hales RE, Yudofsky SC, Talbott JA, eds. *The American Psychiatric Press Textbook of Psychiatry*. 3rd ed. Washington, DC: American Psychiatric Press, 1999.
6. Kay SR, Opler LA, Fiszbein A. *Positive and Negative Syndrome Scale (PANSS). Rating Manual*. New York, 1986.
7. Lindenmayer JP, Bernstein-Hyman R, Grochowski S. A new five factor model of schizophrenia. *Psychiatr Q* 1994;65:299-322.
8. Simpson GM, and Angus JWS. Drug-induced Extrapyramidal Disorders. *Acta Psychiatr Scand* 1970;212:11 - 19.
9. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand* 1970, 212: 11 - 19.
10. Tohen M, Jacobs TG, Feldman PD. Onset of action of antipsychotics in the treatment of mania. *Bipolar Disord* 2000;2(3 Pt 2):261-8.
11. Weissman MM, Bruce ML, Leaf PJ et al. Affective disorders, in *Psychiatric Disorders in America*. Robins L, Regier DA, eds. New York: Free Press, 1990.
12. Potkin, Cohen, Panagides. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry* 2007;68(10):1492–1500
13. Schoemaker, Naber, Vrijland, Panagides, Emsley. Long-term assessment of asenapine vs. olanzapine in patients with schizophrenia or schizoaffective disorder. *Pharmacopsychiatry* 2010; 43(4):138-146
14. Kane, Cohen, Zhao, Alphs, Panagides. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *J Clin Psychopharmacol* 2010;30(2): 106–115
15. Kane, Mackle, Snow-Adami, Zhao, Szegedi, Panagides. A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *J Clin Psychiatry*. 2011;72(3):349-355.
16. McIntyre, Cohen, Zhao, Alphs, Macek, Panagides. Asenapine in the treatment of acute mania in bipolar I disorder: A randomized, double-blind, placebo-controlled trial. *J Affect Disord* 2010; 122(1-2):27–38
17. McIntyre, Cohen, Zhao, Alphs, Macek, Panagides. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar Disord* 2009;11(7):673–686

18. McIntyre, Cohen, Zhao, Alphas, Macek, Panagides. Asenapine versus olanzapine in acute mania: a double-blind extension study. *Bipolar Disord* 2009;11(8):815-826

PART III: CONSUMER INFORMATION**SAPHRIS®****(asenapine sublingual tablets)**

This leaflet is part III of a three-part "Product Monograph" published when SAPHRIS® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SAPHRIS®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

SAPHRIS® (asenapine) sublingual tablet is used to treat schizophrenia and manic or mixed episodes associated with bipolar I disorder in adults.

Schizophrenia is a disease with symptoms such as hearing things, seeing or sensing things that are not there, mistaken beliefs, unusual suspiciousness, becoming withdrawn, incoherent speech and behaviour, and emotional flatness. People with this disease may also feel depressed, anxious, guilty, or tense.

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.

SAPHRIS® is not a cure for your condition, but it can help manage your symptoms and reduce the risk of relapse.

What it does:

SAPHRIS® belongs to a group of medicines called atypical antipsychotic drugs.

Antipsychotic medications affect the chemicals that allow communication between nerve cells (neurotransmitters). Illnesses that affect the brain, such as schizophrenia, may be due to certain chemicals in the brain being out of balance. These imbalances may cause some of the symptoms you may be experiencing. Doctors and scientists are not sure what causes these imbalances to occur. Exactly how SAPHRIS® works is unknown. However, it seems to adjust the balance of chemicals called dopamine and serotonin.

When it should not be used:

Do not take SAPHRIS® if you are allergic (hypersensitive) to asenapine or any of the other ingredients listed in the "Nonmedicinal Ingredients" section of this leaflet. Serious allergic reactions have been observed in patients treated with asenapine. Signs of allergic reaction may include difficulty breathing, rash, itching, swelling of the face, lips, tongue or throat, or feeling lightheaded.

What the medicinal ingredient is:

SAPHRIS® sublingual tablets contain the active ingredient called asenapine.

What the nonmedicinal ingredients are:

SAPHRIS® sublingual tablets contain the following inactive ingredients: gelatin and mannitol.

What dosage forms it comes in:

SAPHRIS® sublingual tablets are available in 5 mg and 10 mg strengths.

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

Various medicines of the group to which SAPHRIS® belongs have been associated with an increased rate of death when used in elderly patients with dementia. SAPHRIS® is not indicated in elderly patients with dementia.

Serious allergic reactions have been observed in patients treated with asenapine. Signs of allergic reaction may include difficulty breathing, rash, itching, swelling of the face, lips, tongue or throat, or feeling lightheaded. In several cases, these reactions occurred after the first dose. Seek immediate emergency assistance if you develop any of these signs or symptoms.

BEFORE you use SAPHRIS® talk to your doctor or pharmacist if you:

- have ever been diagnosed with a condition whose symptoms include high body temperature and muscle stiffness (also known as Neuroleptic Malignant Syndrome)
 - have ever experienced abnormal movements of the tongue or face (also known as Tardive Dyskinesia)
- You should be aware that both of these conditions may be caused by this type of medicine.
- are taking any other medicines (prescription or over the counter medicines)
 - have heart disease, have had a stroke or "mini" stroke, or have a family history of these conditions.
 - are taking a heart disease treatment that makes you prone to low blood pressure
 - are diabetic or prone to diabetes (high blood sugar or family history of diabetes)
 - have epilepsy (seizures)
 - experience any difficulty in swallowing (dysphagia)
 - have severe liver function problems. If you do, you should not take SAPHRIS®.
 - exercise vigorously, work in hot sunny places, or have difficulty controlling core body temperature
 - have thoughts of suicide
 - have an increased level of the hormone prolactin in your blood (hyperprolactinemia)
 - have low white blood cell counts
 - have risk factors for developing blood clots such as: a family history of blood clots, age over 65, smoking,

obesity, recent major surgery (such as hip or knee replacement), immobility due to air travel or other reason, take oral contraceptives ("The Pill")

- drink alcoholic beverages or use recreational drugs
- have ever abused drugs

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 if any of these conditions develops or worsens while using SAPHRIS®.

Asenapine may cause sleepiness, sudden drops in blood pressure when you stand up, dizziness and changes in your ability to move and balance, which may lead to falls and, consequently, fractures or other injuries. Certain medications, diseases or conditions can make this worse. Patients at risk for fall should be evaluated prior to prescribing asenapine.

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

Do not breast-feed when taking SAPHRIS®.

Effects on newborns

In some cases, babies born to a mother taking an antipsychotic medication during pregnancy have experienced symptoms that are severe and require the newborn to be hospitalized. Sometimes, the symptoms may resolve on their own. Be prepared to seek emergency medical attention for your newborn, if he/she has difficulty breathing, is overly sleepy, has muscle stiffness or floppy muscles (like a rag doll), is shaking or is having difficulty feeding.

INTERACTIONS WITH THIS MEDICATION

Tell all doctors, dentists and pharmacists who are treating you that you are taking SAPHRIS®.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should tell your doctor if you are taking antidepressant drugs (specifically fluvoxamine, paroxetine), as it may be necessary to change your SAPHRIS® or antidepressant drug dose.

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

Do not drink alcohol when taking SAPHRIS®.

Only take other medicines while you are on SAPHRIS® if your doctor tells you that you can.

PROPER USE OF THIS MEDICATION

Usual dose:

Always take SAPHRIS® exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is a tablet of 5 or 10 mg two times a day.

Do not remove a tablet until ready to take it. Use dry hands when touching the tablet. Do not push the tablet through the tablet pack. Peel back the colored 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 the tablet. Do not eat or drink for 10 minutes after taking the tablet (Figure 4). When taking SAPHRIS® at the same time as your other oral medication, SAPHRIS® should be taken last and only after having swallowed the other medication and had your drink of water or other liquids.

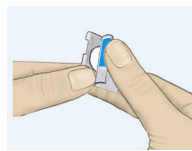


Figure 1

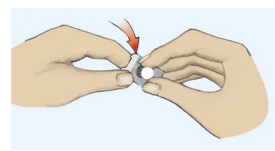


Figure 2

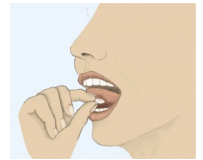


Figure 3



Figure 4

If you stop taking SAPHRIS®, you will lose the effects of this medicine. Even if you feel better, do not stop taking SAPHRIS® or change the times of day you take SAPHRIS® without first consulting your doctor. If your symptoms improve or disappear, it is probably because your treatment is working. SAPHRIS® should be taken for as long as you and your doctor believe it is helping you.

Do not give SAPHRIS® to anyone else. Your doctor has prescribed it for you and your condition. SAPHRIS® is not recommended for use in children under 18 years of age.

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

Overdose:

If you have taken more SAPHRIS® sublingual tablets than your doctor has recommended, contact your regional Poison Control Centre, talk to your doctor right away or go to your nearest hospital emergency department. Take the medication package with you. You may feel agitated and confused.

Missed Dose:

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like other medicines, SAPHRIS® can cause some side effects. These side effects are most likely to be minor and temporary. However, some may be serious and need medical attention.

Serious allergic reactions have been observed in patients treated with asenapine. Signs of allergic reaction may include difficulty breathing, rash, itching, swelling of the face, lips, tongue or throat, or feeling lightheaded. In several cases, these reactions occurred after the first dose. Seek immediate emergency assistance if you develop any of these signs or symptoms.

The most common side effects of SAPHRIS® are:

- sleepiness
- weight gain
- increased appetite
- drowsiness
- restlessness
- slow movements and tremor
- slow or sustained muscle contractions
- dizziness
- change in taste
- involuntary muscle contractions
- sensation of numbness in the tongue or mouth
- fatigue
- increase in the level of liver proteins

Uncommon side effects include:

- 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 or fast heartbeat
- middle heart block
- low blood pressure upon standing
- tingling of the tongue or in the mouth

- swollen face, lips or painful tongue
- difficulty in swallowing
- mouth ulcers or blisters and pain in the mouth

Rare side effects include:

- Neuroleptic malignant syndrome (confusion, reduced or loss of consciousness, high fever, and severe muscle stiffness)
- Serious allergic reactions
- Difficulties in focusing with the eyes
- Increased saliva (drooling)
- Anxiety

Your doctor should check your body weight before starting SAPHRIS® and continue to monitor it for as long as you are being treated.

Your doctor should take blood tests before starting SAPHRIS®. They will monitor blood sugar, and for those with certain risk factors, the number of infection fighting white blood cells. Your doctor should continue to monitor your blood for as long as you are being treated.

If you have high levels of prolactin (measured with a blood test) and a condition called hypogonadism you may be at increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

In the early stages of treatment, some people may faint, or experience symptoms such as light-headedness and dizziness, especially when getting up from a lying or sitting position. This is more likely to happen if you are elderly. This will usually pass on its own but if it does not, tell your doctor.

Falls may occur as a result of one or more adverse events such as: sleepiness, sudden drops in blood pressure when you stand up, dizziness and changes in your ability to move and balance.

SAPHRIS® may affect your concentration or alertness. Make sure these abilities are not affected before you drive or operate machinery.

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.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency help
		Only if severe	In all cases	
Common	Muscle spasm		✓	
	Tremor (involuntary trembling or quivering)		✓	
Uncommon	Pronounced muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion or reduced consciousness			✓
	Seizure (i.e. loss of consciousness with uncontrollable shaking)			✓
	Fainting			✓
	Abnormal movement of tongue or face		✓	
	Difficulty swallowing		✓	
	Allergic reaction (symptoms include difficulty breathing, rash, itching, swelling of the face, lips, tongue, throat, or feeling lightheaded)			✓
	Long-lasting (greater than 4 hours in duration) and painful erection of the penis.			✓
	New or worsening constipation			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency help
		Only if severe	In all cases	
Unknown	Blood clots: swelling, pain and redness in an arm or leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations		✓	

This is not a complete list of side effects. For any unexpected effects while taking SAPHRIS[®], contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.

SAPHRIS[®] should be stored between 2° C to 30° C. Do not use SAPHRIS[®] 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.

REPORTING SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program

Health Canada, Postal Locator 1908C
Ottawa, ON

K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION**If you want more information about SAPHRIS®:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the [Health Canada website](#) or by contacting Organon Canada Inc. at 1-844-820-5468.

This leaflet was prepared by Organon Canada Inc.

Last revised: April 27, 2021.

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