START SAVING TODAY WITH SAPHRIS® SAVINGS PROGRAM

RESTRICTIONS APPLY

Patient Instructions: Redeem this card ONLY when accompanied by a valid prescription for SAPHRIS® (asenapine) sublingual tablets 2.5 mg, 5 mg, and/or 10 mg. A valid Prescriber ID# is required on the prescription. This offer is valid toward out-of-pocket expenses for commercially insured and cash-paying patients filling a SAPHRIS prescription. **Pay the first $25, and we'll pay the rest up to $100 on each of your next 12 prescriptions at your retail pharmacy**. This card is not transferable. By using this card, you confirm that you meet the eligibility criteria and agree to comply with the terms and conditions set forth in the Restrictions section below. Patients with questions, including those with mail order prescriptions, should call **1-855-439-2832**.

Pharmacist Instructions for a Patient with an Eligible Third Party Payer: Submit the claim to the primary Third Party Payer first, then submit the balance due to **Therapy First Plus** as a Secondary Payer as a copay only billing using a valid Other Coverage Code **(eg, 8)**. The patient pay amount will be reduced by $100 after the patient pays the first $25. Reimbursement will be received from **Therapy First Plus**.

Pharmacist Instructions for a Cash-Paying Patient: Submit this claim to **Therapy First Plus**. A valid Other Coverage Code **(eg, 1)** is required. The patient pay amount will be reduced by up to $100 after the patient pays the first $25 and reimbursement will be received from **Therapy First Plus**.

Valid Other Coverage Code Required. For any questions regarding **Therapy First Plus** online processing, call the Help Desk at **1-800-422-5604**.

Restrictions: Offer valid in the U.S. only. Offer not valid for prescriptions reimbursed under Medicaid, a Medicare drug benefit plan, or other federal or state healthcare programs (such as medical assistance programs), or where the patient has secondary coverage for his or her out-of-pocket expenses. If pharmacy benefits are available to the patient for SAPHRIS under any such program, the patient cannot use this card. By presenting or accepting this card, patient and pharmacist each agree not to submit a claim for reimbursement under the above programs. Patient further agrees to comply with any terms of his or her health insurance contract requiring notification to his or her payer of the existence and/or value of this offer. Offer not valid for patients under 10 years of age. For patients between 10 and 17 years of age, an adult must use the card on their behalf. It is illegal to (or offer to) sell, purchase, or trade this card.

Participating patients must have their first card use by **12/31/2016** and their final use by **12/31/2017**. Program managed by PSKW, LLC on behalf of Actavis. This program may be amended or terminated at any time without notice. Product dispensed only pursuant to program rules and federal and state laws. **This is not insurance.**

Please see accompanying full Prescribing Information, including Boxed Warning, on the following pages.

For additional information about SAPHRIS, call Actavis toll-free at 1-800-272-5525.

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Actavis™

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SAPHRIS (asenapine) sublingual tablets safely and effectively. See full prescribing information for SAPHRIS.

SAPHRIS® (asenapine) sublingual tablets
Initial U.S. Approval: 2009

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis. (5.1, 5.2)

----------RECENT MAJOR CHANGES----------

Boxed Warning	10/2014
Indications and Usage (1)	03/2015
Dosage and Administration (2)	03/2015
Contraindications (4)	03/2015
Warnings and Precautions (5)	03/2015

----------INDICATIONS AND USAGE----------

SAPHRIS is an atypical antipsychotic indicated for (1):

- Schizophrenia
- Acute treatment of manic or mixed episodes associated with Bipolar I Disorder as monotherapy or adjunctive treatment to lithium or valproate

----------DOSAGE AND ADMINISTRATION----------

	Starting Dose	Recommended Dose	Maximum Dose
Schizophrenia – acute treatment in adults (2.2)	5 mg sublingually twice daily	5 mg sublingually twice daily	10 mg sublingually twice daily
Schizophrenia – maintenance treatment in adults (2.2)	5 mg sublingually twice daily	5-10 mg sublingually twice daily	10 mg sublingually twice daily
Bipolar mania – adults: monotherapy (2.3)	10 mg sublingually twice daily	5-10 mg sublingually twice daily	10 mg sublingually twice daily
Bipolar mania – pediatric patients (10 to 17 years): monotherapy (2.3)	2.5 mg sublingually twice daily	2.5-10 mg sublingually twice daily	10 mg sublingually twice daily
Bipolar mania – adults: as an adjunct to lithium or valproate (2.3)	5 mg sublingually twice daily	5-10 mg sublingually twice daily	10 mg sublingually twice daily

- Do not swallow tablet. SAPHRIS sublingual tablets should be placed under the tongue and left to dissolve completely. The tablet will dissolve in saliva within seconds. Eating and drinking should be avoided for 10 minutes after administration. (2.1, 17)

----------DOSAGE FORMS AND STRENGTHS----------

Sublingual tablets, black cherry flavor: 2.5 mg, 5 mg and 10 mg (3)

----------CONTRAINDICATIONS----------

- Severe hepatic impairment (Child-Pugh C). (8.7, 12.3)
- Known hypersensitivity to SAPHRIS (asenapine), or to any components in the formulation. (4, 5.6, 17)

----------WARNINGS AND PRECAUTIONS----------

- *Cerebrovascular Adverse Events:* An increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) has been seen in elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs. (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring. (5.3)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate. (5.4)
- *Metabolic Changes:* Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. (5.5)
  - *Hyperglycemia and Diabetes Mellitus:* Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with, and at risk for diabetes. (5.5)
  - *Dyslipidemia:* Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.5)
  - *Weight Gain:* Patients should receive regular monitoring of weight. (5.5)
- *Hypersensitivity Reactions:* Hypersensitivity reactions, including anaphylaxis and angioedema, have been observed. (5.6)
- *Orthostatic Hypotension, Syncope, and Other Hemodynamic Effects:* Dizziness, tachycardia or bradycardia, and syncope may occur, especially early in treatment. Use with caution in patients with known cardiovascular or cerebrovascular disease, and in antipsychotic-naïve patients. (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis* have been reported with antipsychotics. Patients with a pre-existing low white blood cell count (WBC) or a history of 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 a decline in WBC in the absence of other causative factors. (5.8)
- *QT Prolongation:* Increases in QT interval; avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval. (5.9)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.11)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery. (5.12)
- *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder. Closely supervise high-risk patients. (5.14)

----------ADVERSE REACTIONS----------

Commonly observed adverse reactions (incidence ≥5% and at least twice that for placebo) were (6.1):

- *Schizophrenia Adults:* akathisia, oral hypoesthesia, somnolence.
- *Bipolar Disorder Adults (Monotherapy):* somnolence, dizziness, extrapyramidal symptoms other than akathisia, increased weight.
- *Bipolar Disorder Pediatric Patients (Monotherapy):* somnolence, dizziness, dysgeusia, oral paresthesia, nausea, increased appetite, fatigue, increased weight.
- *Bipolar Disorder Adults (Adjunctive):* somnolence, oral hypoesthesia.

To report SUSPECTED ADVERSE REACTIONS, contact Forest Laboratories, LLC. at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Antihypertensive Drugs: SAPHRIS may cause hypotension. (5.7, 7.1, 12.3)
- Paroxetine (CYP2D6 substrate and inhibitor): Reduce paroxetine by half when used in combination with SAPHRIS. (7.1, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- *Pediatric Use:* Safety and efficacy in the treatment of bipolar disorder in patients less than 10 years of age, and patients with schizophrenia ages less than 12 years have not been evaluated. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: March 2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. SAPHRIS® (asenapine) is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1, 5.2)]*.

1 INDICATIONS AND USAGE

SAPHRIS is indicated for:

- Schizophrenia *[see Clinical Studies (14.1)]*
- Acute treatment of manic or mixed episodes associated with Bipolar I disorder as monotherapy or adjunctive treatment to lithium or valproate *[see Clinical Studies (14.2)]*

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

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 split, crushed, chewed, or swallowed *[see Clinical Pharmacology (12.3)]*. Patients should be instructed to not eat or drink for 10 minutes after administration *[see Clinical Pharmacology (12.3) and Patient Counseling Information (17)]*.

2.2 Schizophrenia

The recommended 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. If tolerated, daily dosage can be increased to 10 mg twice daily after one week. The safety of doses above 10 mg twice daily has not been evaluated in clinical studies *[see Clinical Studies (14.1)]*.

2.3 Bipolar I Disorder

Acute Treatment of Manic or Mixed Episodes:

Monotherapy in Adults: The recommended starting dose of SAPHRIS is 10 mg twice daily. The dose can be decreased to 5 mg twice daily if warranted by adverse effects. The safety of doses above 10 mg twice daily has not been evaluated in clinical trials *[see Clinical Studies (14.2)]*.

Monotherapy in Pediatric Patients: The recommended dose of SAPHRIS is 2.5 mg to 10 mg twice daily in pediatric patients 10 to 17 years of age, and dose may be adjusted for individual response and tolerability. The starting dose of SAPHRIS is 2.5 mg twice daily. After 3 days, the dose can be increased to 5 mg twice daily, and from 5 mg to 10 mg twice daily after 3 additional days. Pediatric patients aged 10 to 17 years appear to be more sensitive to dystonia with initial dosing with SAPHRIS when the recommended escalation schedule is not followed *[see Use in Specific Populations (8.4)]*. The safety of doses greater than 10 mg twice daily has not been evaluated in clinical trials *[see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]*.

Adjunctive Therapy in Adults: The recommended starting dose of SAPHRIS is 5 mg twice daily when administered as adjunctive therapy with either lithium or valproate. Depending on the clinical response and tolerability in the individual patient, the dose can be increased to 10 mg twice daily. The safety of doses above 10 mg twice daily as adjunctive therapy with lithium or valproate has not been evaluated in clinical trials.

If SAPHRIS is used for extended periods in bipolar disorder, the health care provider should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

3 DOSAGE FORMS AND STRENGTHS

- SAPHRIS 2.5 mg tablets, black cherry flavor, are round, white to off-white sublingual tablets, with a hexagon on one side.
- SAPHRIS 5 mg tablets, black cherry flavor, are round, white to off-white sublingual tablets, with "5" on one side within a circle.
- SAPHRIS 10 mg tablets, black cherry flavor, are round, white to off-white sublingual tablets, with "10" on one side within a circle.

4 CONTRAINDICATIONS

SAPHRIS is contraindicated in patients with:

- Severe hepatic impairment (Child-Pugh C) *[see Specific Populations (8.7), Clinical Pharmacology (12.3)]*.
- A history of hypersensitivity reactions to asenapine. Reactions have included anaphylaxis and angioedema *[see Warnings and Precautions (5.6), Adverse Reactions (6) and Patient Counseling Information (17)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.2)]*.

5.2 Cerebrovascular Adverse Events, Including Stroke, In Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions (5.1)]*.

5.3 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of 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) 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 antipsychotic drugs 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 regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 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. Whether antipsychotic drug products differ in their potential to cause Tardive Dyskinesia (TD) is unknown.

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 TD 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.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of 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.

Adult Patients: Pooled data from the short-term placebo-controlled schizophrenia and bipolar mania trials are presented in **Table 1**.

TABLE 1: Changes in Fasting Glucose in Adult Patients

	Schizophrenia (6-weeks)				Bipolar (3-weeks)	
		SAPHRIS				SAPHRIS
	Placebo	5 mg twice daily	10 mg twice daily	5 or 10 mg twice daily§	Placebo	5 or 10 mg twice daily†
Mean Change from Baseline in Fasting Glucose at Endpoint						
Change from Baseline (mg/dL) (N*)	-0.2 (232)	3.8 (158)	1.1 (153)	3.2 (377)	-0.6 (89)	-0.6 (156)
Proportion of Patients with Shifts from Baseline to Endpoint						
Normal to High <100 to ≥126 mg/dL (n/N**)	4.1% (7/170)	4.5% (5/111)	4.5% (5/111)	5.0% (13/262)	3.3% (2/61)	2.7% (3/111)
Borderline to High ≥100 and <126 to ≥126 mg/dL (n/N**)	5.9% (3/51)	6.8% (3/44)	6.3% (2/32)	10.5% (10/95)	0.0% (0/23)	11.4% (4/35)

N* = Number of patients who had assessments at both Baseline and Endpoint.
N** = Number of patients at risk at Baseline with assessments at both Baseline and Endpoint.
§ Includes patients treated with flexible dose of SAPHRIS 5 or 10 mg twice daily (N=90).
†SAPHRIS 5 mg or 10 mg twice daily with flexible dosing.

In a 52-week, double-blind, comparator-controlled trial that included primarily patients with schizophrenia, the mean increase from baseline of fasting glucose was 2.4 mg/dL.

Pediatric Patients: Data from the short-term, placebo-controlled trial in pediatric patients with bipolar I disorder are shown in **Table 2**.

TABLE 2: Changes in Fasting Glucose in Pediatric Subjects

	Bipolar I Disorder (3-weeks)			
	Placebo	SAPHRIS 2.5 mg twice daily	SAPHRIS 5 mg twice daily	SAPHRIS 10 mg twice daily
Mean Change from Baseline in Fasting Glucose at Endpoint				
Change from Baseline (mg/dL) (N*)	-2.24 (56)	1.43 (51)	-0.45 (57)	0.34 (52)
Proportion of Subjects with Shifts from Baseline to Endpoint				
Normal to High >45 & <100 to ≥126 mg/dL (n/N*)	0% (0/56)	0% (0/51)	1.8% (1/57)	0% (0/52)

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Adult Patients: Pooled data from the short-term, placebo-controlled schizophrenia and bipolar mania trials are presented in **Table 3**.

TABLE 3: Changes in Lipids in Adult Patients

	Schizophrenia (6-weeks)				Bipolar (3-weeks)	
		SAPHRIS				SAPHRIS
	Placebo	5 mg twice daily	10 mg twice daily	5 or 10 mg twice daily§	Placebo	5 or 10 mg twice daily†
Mean Change from Baseline (mg/dL)						
Total cholesterol (N*)	-2.2 (351)	-2.4 (258)	3.3 (199)	0.4 (539)	-1.5 (163)	1.1 (322)
LDL (N*)	0.1 (285)	-0.2 (195)	2.6 (195)	1.3 (465)	1.9 (158)	1.6 (304)
HDL (N*)	0.5 (290)	0.4 (199)	1.0 (199)	0.5 (480)	0.0 (163)	0.9 (322)
Fasting triglycerides (N*)	-7.6 (233)	-1.9 (159)	0.1 (154)	3.8 (380)	-17.9 (129)	-3.5 (237)
Proportion of Patients with Shifts from Baseline to Endpoint						
Total cholesterol Normal to High <200 to ≥240 (mg/dL) (n/N*)	1.3% (3/225)	0.6% (1/161)	2.2% (3/134)	1.7% (6/343)	1.1% (1/95)	2.5% (5/204)
LDL Normal to High <100 to ≥160 (mg/dL) (n/N*)	1.7% (2/117)	0.0% (0/80)	1.2% (1/86)	1.0% (2/196)	1.9% (1/53)	0.0% (0/141)
HDL Normal to Low ≥40 to <40 (mg/dL) (n/N*)	10.7% (21/196)	13.3% (18/135)	14.7% (20/136)	14.0% (45/322)	7.4% (9/122)	8.7% (21/242)
Fasting triglycerides Normal to High <150 to ≥200 (mg/dL) (n/N*)	2.4% (4/167)	7.0% (8/115)	8.3% (9/108)	7.7% (20/260)	5.1% (4/78)	7.4% (11/148)

N* = Number of subjects who had assessments at both Baseline and Endpoint.
§ Includes subjects treated with flexible dose of SAPHRIS 5 or 10 mg twice daily (N=90).
†SAPHRIS 5 mg or 10 mg twice daily with flexible dosing.

In short-term schizophrenia trials, the proportion of patients with total cholesterol elevations ≥240 mg/dL (at Endpoint) was 8.3% for SAPHRIS-treated patients versus 7% for placebo-treated patients. The proportion of patients with elevations in triglycerides ≥200 mg/dL (at Endpoint) was 13.2% for SAPHRIS-treated patients versus 10.5% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the proportion of patients with total cholesterol elevations ≥240 mg/dL (at Endpoint) was 8.7% for SAPHRIS-treated patients versus 8.6% for placebo-treated patients. The proportion of patients with elevations in triglycerides ≥200 mg/dL (at Endpoint) was 15.2% for SAPHRIS-treated patients versus 11.4% for placebo-treated patients.

In a 52-week, double-blind, comparator-controlled trial that included primarily patients with schizophrenia, the mean decrease from baseline of total cholesterol was 6 mg/dL and the mean decrease from baseline of fasting triglycerides was 9.8 mg/dL.

Pediatric Patients: Data from the short-term, placebo-controlled bipolar mania trial are presented in **Table 4**.

TABLE 4: Changes in Fasting Lipids in Pediatric Subjects

	Bipolar I Disorder (3-weeks)			
	Placebo	SAPHRIS 2.5 mg twice daily	SAPHRIS 5 mg twice daily	SAPHRIS 10 mg twice daily
Mean Change from Baseline (mg/dL)				
Total fasting cholesterol (N*)	-2.3 (57)	3.7 (50)	7.2 (57)	9.3 (52)
Fasting LDL (N*)	-2.5 (57)	-0.2 (50)	3.0 (57)	4.9 (51)
Fasting HDL (N*)	1.6 (57)	2.3 (50)	1.5 (57)	1.7 (52)
Fasting triglycerides (N*)	-6.6 (57)	8.7 (50)	13.4 (57)	14.7 (52)
Proportion of Subjects with Shifts from Baseline to Endpoint				
Total fasting cholesterol Normal to High <170 to >=200 (mg/dL) (n/N*)	1.8% (1/57)	0% (0/50)	1.8% (1/57)	0% (0/52)
Fasting LDL Normal to High <110 to >=130 (n/N*)	1.8% (1/57)	2.0% (1/50)	1.8% (1/57)	0% (0/51)
Fasting HDL Normal to Low ≥40 to <40 (mg/dL) (n/N*)	3.5% (2/57)	6.0% (3/50)	3.5% (2/57)	9.6% (5/52)
Fasting triglycerides Normal to High <150 to ≥200 (mg/dL) (n/N*)	0% (0/57)	4.0% (2/50)	3.5% (2/57)	1.9% (1/52)

N* = Number of patients who had assessments at both Baseline and Endpoint

Weight Gain

Increases in weight have been observed in pre-marketing clinical trials with SAPHRIS. Patients receiving SAPHRIS should receive regular monitoring of weight *[see Patient Counseling Information (17)]*.

Adult Patients: Pooled data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of ≥7% of body weight from the short-term, placebo-controlled schizophrenia and bipolar mania trials are presented in **Table 5**.

Table 5: Change in Body Weight in Adult Patients from Baseline

	Schizophrenia (6-weeks)				Bipolar (3-weeks)	
		SAPHRIS				SAPHRIS
	Placebo	5 mg twice daily	10 mg twice daily	5 or 10 mg twice daily§	Placebo	5 or 10 mg twice daily†
Change from Baseline (kg) (N*)	0.0 (348)	1.0 (251)	0.9 (200)	1.1 (532)	0.2 (171)	1.3 (336)
Proportion of Patients with a ≥7% Increase in Body Weight						
% with ≥7% increase in body weight	1.6%	4.4%	4.8%	4.9%	0.5%	5.8%

N* = Number of subjects who had assessments at both Baseline and Endpoint.
§ Includes subjects treated with flexible dose of SAPHRIS 5 or 10 mg twice daily (N=90).
†SAPHRIS 5 mg or 10 mg twice daily with flexible dosing.

Adult Patients: In a 52-week, double-blind, comparator-controlled adult trial that included primarily patients with schizophrenia, the mean weight gain from baseline was 0.9 kg. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 14.7%. Table 6 provides the mean weight change from baseline and the proportion of patients with a weight gain of ≥7% categorized by Body Mass Index (BMI) at baseline.

Table 6: Weight Change Results Categorized by BMI at Baseline: Comparator-Controlled 52-Week Study in Adults with 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 ≥7% increase in body weight	22%	13%	9%

Pediatric Patients: Data on mean changes in body weight and the proportion of pediatric patients meeting a weight gain criterion of ≥7% of body weight from the short-term, placebo-controlled bipolar mania trial are presented in **Table 7**. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of pediatric patients by comparisons to age- and sex-matched population standards.

The distance of a z-score from 0 represents the distance of a percentile from the median, measured in standard deviations (SD). After adjusting for age and sex, the mean change from baseline to endpoint in weight z-score for SAPHRIS 2.5 mg, 5 mg, and 10 mg twice daily, was 0.11, 0.08 and 0.09 SD versus 0.02 SD for placebo, respectively.

When treating pediatric patients, weight gain should be monitored and assessed against that expected for normal growth.

Table 7: Change in Body Weight in Pediatric Subjects from Baseline

	Bipolar I Disorder (3-weeks)			
	Placebo	SAPHRIS 2.5 mg twice daily	SAPHRIS 5 mg twice daily	SAPHRIS 10 mg twice daily
Change from Baseline (kg) (N*)	0.5 (89)	1.7 (92)	1.6 (90)	1.4 (87)
	Proportion of Subjects with a ≥7% Increase in Body Weight			
% with ≥7% increase in body weight	1.1%	12.0%	8.9%	8.0%

N* = Number of subjects who had assessments at both Baseline and Endpoint.

5.6 Hypersensitivity Reactions

Hypersensitivity reactions have been observed in patients treated with SAPHRIS. In several cases, these reactions occurred after the first dose. These hypersensitivity reactions included: anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue, dyspnea, wheezing and rash.

5.7 Orthostatic Hypotension, Syncope, and Other Hemodynamic Effects

SAPHRIS may induce orthostatic hypotension and syncope in some patients, especially early in treatment, because of its α_1-adrenergic antagonist activity. In short-term schizophrenia adult trials, syncope was reported in 0.2% (1/572) of patients treated with therapeutic doses (5 mg or 10 mg twice daily) of SAPHRIS, compared to 0.3% (1/378) of patients treated with placebo. In short-term bipolar mania adult trials, syncope was reported in 0.3% (1/379) of patients treated with therapeutic doses (5 mg or 10 mg twice daily) of SAPHRIS, compared to 0% (0/203) of patients treated with placebo. During adult pre-marketing clinical trials with SAPHRIS, including long-term trials without comparison to placebo, syncope was reported in 0.6% (11/1953) of patients treated with SAPHRIS. In a 3-week, bipolar mania pediatric trial, syncope was reported in 1% (1/104) of patients treated with SAPHRIS 2.5 mg twice daily, 1% (1/99) of patients treated with SAPHRIS 5 mg twice daily, and 0% (0/99) for patients treated with SAPHRIS 10 mg twice daily compared to 0% (0/101) for 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 (1) patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications); and (2) in the elderly. SAPHRIS should be used cautiously when treating patients who receive treatment with other drugs that can induce hypotension, bradycardia, respiratory or central nervous system depression *[see Drug Interactions (7.1)]*. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs.

5.8 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trial and postmarketing experience, leukopenia and 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)/absolute neutrophil count (ANC) and history of drug induced leukopenia/neutropenia. In patients with a pre-existing low WBC/ANC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of SAPHRIS at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue SAPHRIS in patients with severe neutropenia (absolute neutrophil count <1000/mm^3) and follow their WBC until recovery.

5.9 QT Prolongation

The effects of SAPHRIS on the QT/QTc interval were evaluated in a dedicated adult 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.

5.10 Hyperprolactinemia

Like other drugs that antagonize dopamine D_2 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 SAPHRIS adult clinical trials, the incidences of adverse events related to abnormal prolactin levels were 0.4% versus 0% for placebo. In a 3-week, bipolar mania pediatric trial, the incidence of adverse events related to abnormal prolactin levels were 0% in the SAPHRIS 2.5 mg twice daily treatment group, 2% in the SAPHRIS 5 mg twice daily treatment group, and 1% in the SAPHRIS 10 mg twice daily treatment group versus to 1% for patients treated with placebo *[see Adverse Reactions (6.1)]*.

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.

5.11 Seizures

Seizures were reported in 0% and 0.3% (0/572, 1/379) of adult patients treated with doses of 5 mg and 10 mg twice daily of SAPHRIS, respectively, compared to 0% (0/503, 0/203) of patients treated with placebo in short-term schizophrenia and bipolar mania trials, respectively. During adult pre-marketing clinical trials with SAPHRIS, including long-term trials without comparison to placebo, seizures were reported in 0.3% (5/1953) of patients treated with SAPHRIS. There were no reports of seizures in pediatric patients treated with SAPHRIS in a 3-week-term, bipolar mania trial.

As with other antipsychotic drugs, SAPHRIS should be used with caution in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

5.12 Potential for Cognitive and Motor Impairment

Somnolence was reported in patients treated with SAPHRIS. It was usually transient with the highest incidence reported during the first week of treatment. In short-term, fixed-dose, placebo-controlled schizophrenia adult trials, somnolence 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 adult trials of therapeutic doses (5-10 mg twice daily), somnolence was reported in 24% (90/379) of patients on SAPHRIS compared to 6% (13/203) of placebo patients. During adult pre-marketing clinical trials with SAPHRIS, including long-term trials without comparison to placebo, somnolence was reported in 18% (358/1953) of patients treated with SAPHRIS. Somnolence (including sedation) led to discontinuation in 0.6% (12/1953) of patients in short-term, placebo-controlled trials.

In a 3-week, placebo-controlled, bipolar I pediatric trial, the incidence of somnolence (including sedation and hypersomnia) for placebo, SAPHRIS 2.5 mg twice daily, 5 mg twice daily, and 10 mg twice daily, was 12% (12/101), 46% (48/104), 53% (52/99), and 49% (49/99), respectively. Somnolence led to discontinuation in 0%, 3%, 1%, and 2% of patients treated with placebo, and SAPHRIS 2.5 mg twice daily, 5 mg twice daily, and 10 mg twice daily, respectively.

Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that SAPHRIS therapy does not affect them adversely.

5.13 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. In the short-term placebo-controlled trials for both schizophrenia and acute bipolar disorder, the incidence of adverse reactions suggestive of body temperature increases was low (≤1%) and comparable to placebo (0%). During clinical trials with SAPHRIS, including long-term trials without comparison to placebo, the incidence of adverse reactions suggestive of body temperature increases (pyrexia and feeling hot) was ≤1%.

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.

5.14 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. Prescriptions for SAPHRIS should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

5.15 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Dysphagia was reported in 0.2% and 0% (1/572, 0/379) of patients treated with therapeutic doses (5-10 mg twice daily) of SAPHRIS as compared to 0% (0/378, 0/203) of patients treated with placebo in short-term schizophrenia and bipolar mania adult trials, respectively. During adult pre-marketing clinical trials with SAPHRIS, including long-term trials without comparison to placebo, dysphagia was reported in 0.1% (2/1953) of 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 is not indicated for the treatment of dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia *[see also Warnings and Precautions (5.1)]*.

5.16 Use in Patients with Concomitant Illness

Clinical experience with SAPHRIS in patients with certain concomitant systemic illnesses is limited *[see Clinical Pharmacology (12.3)]*.

SAPHRIS has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from pre-marketing clinical trials. Because of the risk of orthostatic hypotension with SAPHRIS, caution should be observed in cardiac patients *[see Warnings and Precautions (5.7)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Use in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1 and 5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Metabolic Changes *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions *[see Contraindications, Warnings and Precautions (5.6) and Patient Counseling Information (17)]*
- Application site reactions including oral ulcers, blisters, peeling/sloughing and inflammation *[see Adverse Reactions (6.2)]*
- Orthostatic Hypotension, Syncope, and other Hemodynamic Effects *[see Warnings and Precautions (5.7)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.8)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.9)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.12)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.13)]*
- Suicide *[see Warnings and Precautions (5.14)]*
- Dysphagia *[see Warnings and Precautions (5.15)]*
- Use in Patients with Concomitant Illness *[see Warnings and Precautions (5.16)]*

The most common adverse reactions (≥5% and at least twice the rate of placebo) reported with acute treatment in adults with schizophrenia were akathisia, oral hypoesthesia, and somnolence. The safety profile of SAPHRIS in the maintenance treatment of schizophrenia in adults was similar to that seen with acute treatment.

The most common adverse reactions (≥5% and at least twice the rate of placebo) reported with acute monotherapy treatment of manic or mixed episodes associated with bipolar I disorder in adults were somnolence, dizziness, extrapyramidal symptoms other than akathisia, and increased weight and during the adjunctive therapy trial in bipolar I disorder in adults were somnolence and oral hypoesthesia.

The adult information below is derived from a clinical trial database for SAPHRIS consisting of over 4565 patients and/or healthy subjects exposed to one or more sublingual doses of SAPHRIS. A total of 1314 SAPHRIS-treated patients were treated for at least 24 weeks and 785 SAPHRIS-treated patients had at least 52 weeks of exposure at therapeutic doses.

In a 3-week monotherapy trial, the most common adverse reactions (≥5% and at least twice the rate of placebo) reported in pediatric patients with bipolar I disorder treated with SAPHRIS were somnolence, dizziness, dysgeusia, oral paresthesia, nausea, increased appetite, fatigue, and increased weight. No new major safety findings were reported from a 50-week, open-label, uncontrolled safety trial.

A total of 651 pediatric patients were treated with SAPHRIS. Of these patients, 352 pediatric patients were treated with SAPHRIS for at least 180 days and 58 pediatric patients treated with SAPHRIS had at least 1 year of exposure. The safety of SAPHRIS was evaluated in 403 pediatric patients with bipolar I disorder who participated in a 3-week, placebo-controlled, double-blind trial, of whom 302 patients received SAPHRIS at fixed doses ranging from 2.5 mg to 10 mg twice daily.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced a treatment-emergent adverse event of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Patients with Schizophrenia: The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of three 6-week fixed-dose trials and one 6-week flexible-dose trial) in which sublingual SAPHRIS was administered in doses ranging from 5 to 10 mg twice daily.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9% of SAPHRIS-treated patients and 10% of placebo-treated patients discontinued due to adverse reactions. There were no drug-related adverse reactions associated with discontinuation in patients treated with SAPHRIS at the rate of at least 1% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in SAPHRIS-Treated Patients with Schizophrenia: Adverse reactions associated with the use of SAPHRIS (incidence of 2% or greater, rounded to the nearest percent, and SAPHRIS incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in patients with schizophrenia) are shown in **Table 8**.

Table 8: Adverse Reactions Reported in 2% or More of Adult Patients in Any SAPHRIS Dose Group 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				
Increased weight	<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 Reactions: In the short term schizophrenia trials the incidence of akathisia appeared to be dose-related (see Table 8).

Monotherapy in Adult Patients with Bipolar Mania: The following findings are based on the short-term placebo-controlled trials for bipolar mania (a pool of two 3-week flexible-dose trials) in which sublingual SAPHRIS was administered in doses of 5 mg or 10 mg twice daily.

Adverse Reactions Associated with Discontinuation of Treatment: Approximately 10% (38/379) of SAPHRIS-treated patients in short-term, placebo-controlled trials discontinued treatment due to an adverse reaction, compared with about 6% (12/203) on placebo. The most common adverse reactions associated with discontinuation in patients 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%).

Adverse Reactions Occurring at an Incidence of 2% or More Among SAPHRIS-Treated (Monotherapy) patients with Bipolar I Disorder: Adverse reactions associated with the use of SAPHRIS (incidence of 2% or greater, rounded to the nearest percent, and SAPHRIS incidence greater than placebo) that occurred during acute monotherapy (up to 3-weeks in patients with bipolar mania) are shown in **Table 9**.

Table 9: Adverse Reactions Reported in 2% or More of Adult Patients in Any SAPHRIS Dose Group and Which Occurred at Greater Incidence Than in the Placebo Group in 3-Week Bipolar Mania Trials

System Organ Class/Preferred Term	Placebo N=203 %	SAPHRIS 5 mg or 10 mg twice daily* N=379 %
Gastrointestinal disorders		
Dry mouth	1	3
Dyspepsia	2	4
Oral hypoesthesia	<1	4
Toothache	2	3
General disorders		
Fatigue	2	4
Investigations		
Increased weight	<1	5
Metabolism disorders		
Increased appetite	1	4
Musculoskeletal and connective tissue disorders		
Arthralgia	1	3
Pain in extremity	<1	2
Nervous system disorders		
Akathisia	2	4
Dizziness	3	11
Dysgeusia	<1	3
Headache	11	12
Other extrapyramidal symptoms (excluding akathisia)†	2	7
Somnolence‡	6	24
Psychiatric disorders		
Anxiety	2	4
Depression	1	2
Insomnia	5	6

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

† Extrapyramidal symptoms included: 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.

Monotherapy in Pediatric Patients with Bipolar Mania: The following findings are based on a 3-week, placebo-controlled trial for bipolar mania in which SAPHRIS was administered at doses of 2.5 mg, 5 mg, or 10 mg twice daily.

Adverse Reactions Leading to Discontinuation of Treatment: A total of 6.7% (7/104) of patients treated with SAPHRIS 2.5 mg twice daily, 5.1% (5/99) of patients treated with SAPHRIS 5 mg twice daily, and 5.1% (5/99) of patients treated with SAPHRIS 10 mg twice daily discontinued treatment due to adverse reactions compared to 4% (4/101) on placebo. The most common adverse reactions that led to discontinuation in pediatric patients treated with SAPHRIS (rates at least 2% in any SAPHRIS arm and at least twice the placebo rate) were somnolence (3% in the 2.5 mg twice daily group, 1% in the 5 mg twice daily group, and 2% in the 10 mg twice daily group), abdominal pain (2% in the 10 mg twice daily group), and nausea (2% in the 10 mg twice daily group). No placebo-treated patients dropped out for these events.

Adverse Reactions Occurring with SAPHRIS at an Incidence of 2% or More in SAPHRIS-treated Bipolar Patients: Adverse reactions associated with the use of SAPHRIS (incidence of ≥2% in any SAPHRIS dose group and greater than placebo) that occurred during acute therapy are shown in **Table 10**.

Table 10: Adverse Reactions Reported in 2% or More of Pediatric Patients (Ages 10 to 17 Years) in Any SAPHRIS Dose Group and Which Occurred at Greater Incidence Than in the Placebo Group in a 3-Week Bipolar Mania Trial

System Organ Class/ AE Preferred Term	Placebo	SAPHRIS 2.5 mg twice daily	SAPHRIS 5 mg twice daily	SAPHRIS 10 mg twice daily	All SAPHRIS 2.5, 5, and 10 mg
	N=101 %	N=104 %	N=99 %	N=99 %	N=302 %
Cardiac Disorders					
Tachycardia[1]	0	3	0	1	1
Gastrointestinal Disorders					
Oral paraesthesia[2]	4	25	25	30	27
Nausea	3	6	6	6	6
Vomiting	3	4	4	4	4
Abdominal pain[3]	7	9	3	5	6
Glossodynia	0	0	2	0	1
General Disorders and Administrative Site Disorders					
Fatigue[4]	5	4	8	14	9
Irritability	1	1	1	2	1
Injury, Poisoning, and Procedural Complications					
Muscle strain	0	0	0	2	1
Investigations					
Increased weight	0	6	2	2	3
Hyperinsulinemia[5]	0	1	3	1	2
ALT increased	0	0	0	2	1
AST increased	0	0	0	2	1
Metabolism and Nutrition Disorders					
Increased appetite	2	10	9	6	8
Dehydration	1	0	2	0	1
Musculoskeletal and Connective Tissue Disorders					
Myalgia	0	0	2	1	1
Nervous System Disorders					
Somnolence[6]	12	46	53	49	49
Headache	6	8	11	9	9
Dizziness	3	6	10	5	7
Dysgeusia	2	4	5	9	6
Akathisia	0	2	2	1	2
Parkinsonism	0	1	0	2	1
Psychiatric Disorders					
Insomnia	3	3	4	3	3
Suicidal ideation	1	4	1	3	3
Anger	0	0	0	2	1
Reproductive System and Breast Disorders					
Dysmenorrhea	1	0	2	0	1
Respiratory, Thoracic, and Mediastinal Disorders					
Oropharyngeal pain	2	0	3	1	1
Nasal congestion	1	0	2	0	1
Dyspnea	0	0	2	0	1
Skin and Subcutaneous Tissue Disorders					
Rash	1	0	1	2	1

[1] Includes the preferred terms tachycardia and heart rate increased.

[2] Includes the preferred terms oral hypoesthesia, oral paresthesia, and oral dysesthesia.

[3] Includes the preferred terms abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

[4] Includes the preferred terms fatigue and lethargy.

[5] Includes the preferred terms hyperinsulinemia and blood insulin increased.

[6] Includes the preferred terms somnolence, sedation, and hypersomnia.

Dose-Related Adverse Reactions: In the short term pediatric bipolar trials the incidence of fatigue appeared to be dose-related (see **Table 10**).

Adjunctive Therapy in Adult Patients with Bipolar Mania: The following findings are based on a 12 week placebo-controlled trial (with a 3 week efficacy endpoint) in adult patients with bipolar mania in which sublingual SAPHRIS was administered in doses of 5 mg or 10 mg twice daily as adjunctive therapy with lithium or valproate.

Adverse Reactions Associated with Discontinuation of Treatment: Approximately 16% (25/158) of SAPHRIS-treated patients discontinued treatment due to an adverse reaction, compared with about 11% (18/166) 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%).

Adverse Reactions Occurring at an Incidence of 2% or More Among SAPHRIS-Treated (Adjunctive) Bipolar Patients: Adverse reactions associated with the use of SAPHRIS (incidence of 2% or greater, rounded to the nearest percent, and SAPHRIS incidence greater than placebo) that occurred during acute adjunctive therapy at 3 weeks, a time when most of the patients were still participating in the trial, are shown in **Table 11**.

Table 11: Adverse Reactions Reported in 2% or More of Adult Patients In Any SAPHRIS-Dose Group and Which Occurred at Greater Incidence Than in the Placebo Group at 3 Weeks in Adjunctive Bipolar Mania Trials

System Organ Class/Preferred Term	Placebo N=166 %	SAPHRIS 5 mg or 10 mg twice daily* N=158 %
Gastrointestinal disorders		
Dyspepsia	2	3
Oral hypoesthesia	0	5
General disorders		
Fatigue	2	4
Edema peripheral	<1	3
Investigations		
Increased weight	0	3
Nervous system disorders		
Dizziness	2	4
Other extrapyramidal symptoms (excluding akathisia)†	5	6
Somnolence‡	10	22
Psychiatric disorders		
Insomnia	8	10
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.

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 *[see Dosage and Administration (2.3), Use in Specific Populations (8.4), and Clinical Pharmacology (12.3)]*.

Extrapyramidal Symptoms: In the short-term, placebo-controlled schizophrenia and bipolar mania adult trials, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). 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.

In the short-term, placebo-controlled schizophrenia adult trials, the incidence of reported EPS-related events, excluding events related to akathisia, for SAPHRIS-treated patients was 10% versus 7% for placebo; and the incidence of akathisia-related events for SAPHRIS-treated patients was 6% versus 3% for placebo. In short-term placebo-controlled bipolar mania adult trials, the incidence of EPS-related events, excluding events related to akathisia, for SAPHRIS-treated patients was 7% versus 2% for placebo; and the incidence of akathisia-related events for SAPHRIS-treated patients was 4% versus 2% for placebo.

In a 3-week, placebo-controlled pediatric trial with bipolar I disorder, the incidences of EPS-related events, excluding events related to akathisia, were 4%, 3%, and 5% for patients treated with SAPHRIS 2.5 mg, 5 mg, and 10 mg twice daily, respectively, as compared to 3% for placebo-treated patients. EPS-related events include: bradykinesia, dyskinesia, dystonia, oromandibular dystonia, muscle contractions involuntary, muscle twitching, musculoskeletal stiffness, parkinsonism, protrusion tongue, resting tremor, and tremor.

For events of akathisia, incidences were 2%, 2%, and 1% for patients treated with SAPHRIS 2.5 mg, 5 mg, and 10 mg twice daily, respectively, as compared to 0% for placebo-treated patients.

Other Findings: Oral hypoesthesia and/or oral paresthesia may occur directly after administration of SAPHRIS and usually resolves within 1 hour.

Laboratory Test Abnormalities:

Transaminases: Transient elevations in serum transaminases (primarily ALT) in the short-term schizophrenia and bipolar mania adult trials were more common in treated patients. In short-term, placebo-controlled schizophrenia adult trials, the mean increase in transaminase levels for SAPHRIS-treated patients was 1.6 units/L compared to a decrease of 0.4 units/L for placebo-treated patients. The proportion of patients with transaminase elevations ≥3 times ULN (at Endpoint) was 0.9% for SAPHRIS-treated patients versus 1.3% for placebo-treated patients. In short-term, placebo-controlled bipolar adult 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 Endpoint) was 2.5% for SAPHRIS-treated patients versus 0.6% for placebo-treated patients.

In a 52-week, double-blind, comparator-controlled trial that included primarily adult patients with schizophrenia, the mean increase from baseline of ALT was 1.7 units/L.

In a 3-week, placebo-controlled pediatric trial with bipolar I disorder, transient elevations in serum transaminases (primarily ALT) were more common in treated patients. The proportion of pediatric patients with ALT elevations ≥3 times upper limit of normal (ULN) was 2.4% for patients treated with SAPHRIS 10 mg twice daily versus none for the other SAPHRIS dose groups and placebo-treated patients.

Prolactin: In short-term, placebo-controlled adult schizophrenia trials, the mean decreases in prolactin levels were 6.5 ng/mL for SAPHRIS-treated patients compared to 10.7 ng/mL for placebo-treated patients. The proportion of patients with prolactin elevations ≥4 times ULN (at Endpoint) were 2.6% for SAPHRIS-treated patients versus 0.6% for placebo-treated patients. In short-term, placebo-controlled bipolar mania adult trials, the mean increase in prolactin levels was 4.9 ng/mL for SAPHRIS-treated patients compared to a decrease of 0.2 ng/mL for placebo-treated patients. The proportion of patients with prolactin elevations ≥4 times ULN (at Endpoint) were 2.3% for SAPHRIS-treated patients versus 0.7% for placebo-treated patients.

In a long-term (52-week), double-blind, comparator-controlled adult trial that included primarily patients with schizophrenia, the mean decrease in prolactin from baseline for SAPHRIS-treated patients was 26.9 ng/mL.

In a 3-week, placebo-controlled pediatric trial with bipolar I disorder, the mean increases (at Endpoint) in prolactin levels were 3.2 ng/mL for patients treated with SAPHRIS 2.5 mg twice daily, 2.1 ng/mL for patients treated with SAPHRIS 5 mg twice daily, and 6.4 ng/mL for patients treated with SAPHRIS 10 mg twice daily compared to an increase of 2.5 ng/mL for placebo-treated patients. There were no reports of prolactin elevations ≥4 times ULN (at Endpoint) for patients treated with SAPHRIS or placebo. Galactorrhea or dysmenorrhea were reported in 0% of patients treated with SAPHRIS 2.5 mg twice daily, 2% of patients treated with SAPHRIS 5 mg twice daily, and 1% of patients treated with SAPHRIS 10 mg twice daily compared to 1% of placebo-treated patients. There were no reports of gynecomastia in this trial.

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.

The proportion of patients with CK elevations ≥3 times ULN during a 3-week trial in pediatric bipolar I disorder at any time were 1%, 0%, and 1% for patients treated with SAPHRIS 2.5 mg, 5 mg, and 10 mg twice daily, respectively, versus 3% for placebo-treated patients.

Other Adverse Reactions Observed During the Premarketing Evaluation of SAPHRIS: Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with sublingual SAPHRIS at multiple doses of ≥5 mg twice daily during any phase of a trial within the database of adult patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions already listed for either adults or pediatric patients in other parts of *Adverse Reactions (6)*, or those considered in *Contraindications (4), Warnings and Precautions (5) or Overdosage (10)* are not included. Reactions are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Blood and lymphatic disorders: infrequent: anemia; *rare:* thrombocytopenia
Cardiac disorders: infrequent: temporary bundle branch block
Eye disorders: infrequent: accommodation disorder
Gastrointestinal disorders: infrequent: swollen tongue
General disorders: rare: idiosyncratic drug reaction
Investigations: infrequent: hyponatremia
Nervous system disorders: infrequent: dysarthria

Following is a list of MedDRA terms not already listed either for adults or pediatric patients in other parts of *Adverse Reactions (6)*, or those considered in *Contraindications (4), Warnings and Precautions (5)* or *Overdosage (10)* that reflect adverse reactions reported by pediatric patients (Ages 10 to 17 years) treated with sublingual SAPHRIS at doses of 2.5 mg, 5 mg, or 10 mg twice daily during any phase of a trial within the database of pediatric patients.

Eye disorders: infrequent: diplopia, vision blurred
Gastrointestinal disorders: infrequent: gastroesophageal reflux disease
Injury, Poisoning, and Procedural Complications: infrequent: fall
Skin and subcutaneous tissue disorders: infrequent: photosensitivity reaction
Renal and urinary disorders: infrequent: enuresis

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SAPHRIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure. In many cases, the occurrence of these adverse reactions led to discontinuation of therapy.

- Application site reactions, primarily in the sublingual area, have been reported. These application site reactions included oral ulcers, blisters, peeling/sloughing, and inflammation.
- Choking has been reported by patients, some of whom may have also experienced oropharyngeal muscular dysfunction or hypoesthesia.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Drug Interactions with SAPHRIS

Table 12: Clinically Important Drug Interactions with SAPHRIS

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Antihypertensive Drugs	Because of its α_1-adrenergic antagonism with potential for inducing hypotension, SAPHRIS may enhance the effects of certain antihypertensive agents *[see Warnings and Precautions (5.7)]*.	Monitor blood pressure and adjust dosage of antihypertensive drug accordingly.
Strong CYP1A2 Inhibitors (e.g., Fluvoxamine)	SAPHRIS is metabolized by CYP1A2. Marginal increase of asenapine exposure was observed when SAPHRIS is used with fluvoxamine at 25 mg administered twice daily *[see Clinical Pharmacology (12.3)]*. However, the tested fluvoxamine dose was suboptimal. Full therapeutic dose of fluvoxamine is expected to cause a greater increase in asenapine exposure.	Dosage reduction for SAPHRIS based on clinical response may be necessary.
CYP2D6 substrates and inhibitors (e.g., paroxetine)	SAPHRIS may enhance the inhibitory effects of paroxetine on its own metabolism. Concomitant use of paroxetine with SAPHRIS increased the paroxetine exposure by 2-fold as compared to use paroxetine alone *[see Clinical Pharmacology (12.3)]*.	Reduce paroxetine dose by half when paroxetine is used in combination with SAPHRIS.

7.2 Drugs Having No Clinically Important Interactions with SAPHRIS

No dosage adjustment of SAPHRIS is necessary when administered concomitantly with paroxetine (see Table 12 in Drug Interactions (7.1) for paroxetine dosage adjustment), imipramine, cimetidine, valporate, lithium, or a CYP3A4 inducer (e.g., carbamazepine, phenytoin, rifampin).

In addition, valproic acid and lithium pre-dose serum concentrations collected from an adjunctive therapy study were comparable between asenapine-treated patients and placebo-treated patients indicating a lack of effect of asenapine on valproic and lithium plasma levels.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SAPHRIS during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. Studies have not been conducted with SAPHRIS in pregnant women. There are no available human data informing the drug-associated risk. The background risk of major birth defects and miscarriage for the indicated populations are unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies. No teratogenicity was observed in animal reproduction studies with intravenous administration of asenapine to rats and rabbits during organogenesis at doses 0.7 and 0.4 times, respectively, the maximum recommended human dose (MRHD) of 10 mg sublingually twice daily. In a pre-and post-natal study in rats, intravenous administration of asenapine at doses up to 0.7 times the MRHD produced increases in post-implantation loss and early pup deaths, and decreases in subsequent pup survival and weight gain *[see Data]*. Advise pregnant women of the potential risk to a fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

Data

Animal Data

In animal studies, asenapine increased post-implantation loss and decreased pup weight and survival at doses similar to or less than recommended clinical doses. In these studies there was no increase in the incidence of structural abnormalities caused by asenapine.

Asenapine was not teratogenic in reproduction studies in rats and rabbits at intravenous doses up to 1.5 mg/kg in rats and 0.44 mg/kg in rabbits administered during organogenesis. These doses are 0.7 and 0.4 times, respectively, the maximum recommended human dose (MRHD) of 10 mg twice daily given sublingually on a mg/m^2 basis. Plasma levels of asenapine were measured in the rabbit study, and the area under the curve (AUC) at the highest dose tested was 2 times that in humans receiving the MRHD.

In a study in which rats were treated from day 6 of gestation through day 21 postpartum with intravenous doses of asenapine of 0.3, 0.9, and 1.5 mg/kg/day (0.15, 0.4, and 0.7 times the MRHD of 10 mg twice daily given sublingually on a mg/m^2 basis), increases in post-implantation loss and early pup deaths were seen at all doses, and decreases in subsequent pup survival and weight gain were seen at the two higher doses. A cross-fostering study indicated that the decreases in pup survival were largely due to prenatal drug effects. Increases in post-implantation loss and decreases in pup weight and survival were also seen when pregnant rats were dosed orally with asenapine.

8.2 Lactation

Risk Summary

Lactation studies have not been conducted to assess the presence of asenapine in human milk, the effects of asenapine on the breastfed infant, or the effects of asenapine on milk production. Asenapine is excreted in rat milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for SAPHRIS and any potential adverse effects on the breastfed infant from SAPHRIS or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy of SAPHRIS in pediatric patients below the age of 10 years of age have not been evaluated.

Bipolar I Disorder

The safety and efficacy of SAPHRIS as monotherapy in the treatment of bipolar I disorder were established in a 3-week, placebo-controlled, double-blind trial of 403 pediatric patients 10 to 17 years of age, of whom 302 patients received SAPHRIS at fixed doses ranging from 2.5 mg to 10 mg twice daily *[see Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*. In a Phase 1 study, pediatric patients aged 10 to 17 years appeared to be more sensitive to dystonia with initial dosing with asenapine when the recommended dose escalation schedule was not followed. No new major safety findings were reported from a 50-week, open-label, uncontrolled safety trial in pediatric patients with bipolar disorder treated with SAPHRIS monotherapy. The safety and efficacy of SAPHRIS as adjunctive therapy in the treatment of bipolar I disorder have not been established in the pediatric population. In general, the pharmacokinetics of asenapine in pediatric patients (10 to 17 years) and adults are similar *[see Clinical Pharmacology (12.3)]*.

Schizophrenia

Efficacy of SAPHRIS was not demonstrated in an 8-week, placebo-controlled, double-blind trial, in 306 adolescent patients aged 12 to 17 years with schizophrenia at doses of 2.5 and 5 mg twice daily. The most common adverse reactions (proportion of patients equal or greater than 5% and at least twice placebo) reported were somnolence, akathisia, dizziness, and oral hypoesthesia or paresthesia. The proportion of patients with an equal or greater than 7% increase in body weight at endpoint compared to baseline for placebo, SAPHRIS 2.5 mg twice daily, and SAPHRIS 5 mg twice daily was 3%, 10%, and 10%, respectively.

The clinically relevant adverse reactions identified in the pediatric schizophrenia trial were generally similar to those observed in the pediatric bipolar and adult bipolar and schizophrenia trials. No new major safety findings were reported from a 26-week, open-label, uncontrolled safety trial in pediatric patients with schizophrenia treated with SAPHRIS monotherapy.

Juvenile Animal Data

Subcutaneous administration of asenapine to juvenile rats for 56 days from day 14 of age to day 69 of age at 0.4, 1.2, and 3.2 mg/kg/day (0.2, 0.6 and 1.5 times the maximum recommended human dose of 10 mg twice daily given sublingually on a mg/m^2 basis) resulted in significant reduction in body weight gain in animals of both sexes at all dose levels from the start of dosing until weaning. Body weight gain remained reduced in males to the end of treatment, however, recovery was observed once treatment ended. Neurobehavioral assessment indicated increased motor activity in animals at all dose levels following the completion of treatment, with the evidence of recovery in males. There was no recovery after the end of treatment in female activity pattern as late as day 30 following the completion of treatment (last retesting). Therefore, a No Observed Adverse Effect Level (NOAEL) for the juvenile animal toxicity of asenapine could not be determined. There were no treatment-related effects on the startle response, learning/memory, organ weights, microscopic evaluations of the brain and, reproductive performance (except for minimally reduced conception rate and fertility index in males and females administered 1.2 and 3.2 mg/kg/day).

8.5 Geriatric Use

Clinical studies of SAPHRIS in the treatment of schizophrenia and bipolar mania did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Of the approximately 2250 patients in pre-marketing clinical studies of SAPHRIS, 1.1% (25) were 65 years of age or over. Multiple factors that might increase the pharmacodynamic response to SAPHRIS, causing poorer tolerance or orthostasis, could be present in elderly patients, and these patients should be monitored carefully. Based on a pharmacokinetic study in elderly patients, dosage adjustments are not recommended based on age alone *[see Clinical Pharmacology (12.3)]*.

Elderly patients with dementia-related psychosis treated with SAPHRIS are at an increased risk of death compared to placebo. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

8.6 Renal Impairment

No dosage adjustment for SAPHRIS is required on the basis of a patient's renal function (mild to severe renal impairment, glomerular filtration rate between 15 and 90 mL/minute). The exposure of asenapine was similar among subjects with varying degrees of renal impairment and subjects with normal renal function *[see Clinical Pharmacology (12.3)]*. The effect of renal function on the excretion of other metabolites and the effect of dialysis on the pharmacokinetics of asenapine has not been studied.

8.7 Hepatic Impairment

SAPHRIS is contraindicated in patients with severe hepatic impairment (Child-Pugh C) because asenapine exposure is 7-fold higher in subjects with severe hepatic impairment than the exposure observed in subjects with normal hepatic function.

No dosage adjustment for SAPHRIS is required in patients with mild to moderate hepatic impairment (Child-Pugh A and B) because asenapine exposure is similar to that in subjects with normal hepatic function *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

8.8 Other Specific Populations

No dosage adjustment for SAPHRIS is required on the basis of a patient's sex, race (Caucasian and Japanese), or smoking status *[see Cllinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

SAPHRIS is not a controlled substance.

9.2 Abuse

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).

10 OVERDOSAGE

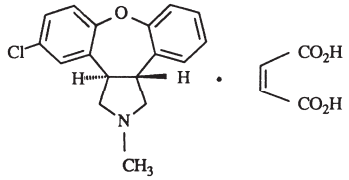
Human Experience: In adult pre-marketing clinical studies involving more than 3350 patients and/or healthy subjects, accidental or intentional acute overdosage of SAPHRIS was identified in 3 patients. Among these few reported cases of overdose, the highest estimated ingestion of SAPHRIS was 400 mg. Reported adverse reactions at the highest dosage included agitation and confusion.

Management of Overdosage: There is no specific antidote to SAPHRIS. The possibility of multiple drug involvement should be considered. An electrocardiogram should be obtained and management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Consult with a Certified Poison Control Center for up-to-date guidance and advice on the management of overdosage (1-800-222-1222.)

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 stimulation 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.

11 DESCRIPTION

SAPHRIS contains asenapine maleate which is a psychotropic agent that is available for sublingual administration. Asenapine belongs to the class dibenzo-oxepino pyrroles. The chemical designation is (3a*RS*,12b*RS*)-5-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*dibenzo[2,3:6,7]oxepino[4,5-*c*]pyrrole (2*Z*)-2-butenedioate (1:1). Its molecular formula is $C_{17}H_{16}ClNO \cdot C_4H_4O_4$ and its molecular weight is 401.84 (free base: 285.8). The chemical structure is:



Asenapine maleate is a white to off-white powder.

SAPHRIS, black cherry flavor, is supplied for sublingual administration in tablets containing 2.5 mg, 5 mg or 10 mg asenapine; inactive ingredients include gelatin, mannitol, sucralose, and black cherry flavor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of asenapine, in schizophrenia and bipolar disorder, is unknown. It has been suggested that the efficacy of asenapine in schizophrenia could be mediated through a combination of antagonist activity at D_2 and 5-HT_{2A} receptors.

12.2 Pharmacodynamics

Asenapine exhibits high affinity for serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_{5A}, 5-HT_6, and 5-HT_7 receptors (Ki 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}, D_3, D_4, and D_1 receptors (Ki 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 (Ki values of 1.2, 1.2, 0.33 and 1.2 nM, respectively), and histamine H_1 receptors (Ki value 1.0 nM), and moderate affinity for H_2 receptors (Ki value of 6.2 nM). In *in vitro* assays asenapine acts as an antagonist at these receptors. Asenapine has no appreciable affinity for muscarinic cholinergic receptors (e.g., Ki value of 8128 nM for M_1).

12.3 Pharmacokinetics

Following a single 5 mg dose of SAPHRIS, the mean C_{max} was approximately 4 ng/mL and was observed at a mean t_{max} of 1 hour. Elimination of asenapine is primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2). Following an initial more rapid distribution phase, the mean terminal half-life is approximately 24 hrs. With multiple-dose twice-daily dosing, steady-state is attained within 3 days. Overall, steady-state asenapine pharmacokinetics are similar to single-dose 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 35%. Increasing the dose from 5 mg to 10 mg twice daily (a two-fold increase) results in less than linear (1.7 times) increases in both the extent of exposure and maximum concentration. The absolute bioavailability of asenapine when swallowed is low (<2% with an oral tablet formulation).

The intake of water several (2 or 5) minutes after asenapine administration resulted in decreased asenapine exposure. Therefore, eating and drinking should be avoided for 10 minutes after administration *[see Dosage and Administration (2.1)]*.

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 Elimination: 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. Steady-state concentrations of asenapine are reached within 3 days of twice daily dosing.

After administration of a single dose of [^{14}C]-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-desmethylasenapine, N-desmethylasenapine N-carbamoyl glucuronide, and unchanged asenapine in smaller amounts. SAPHRIS 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 (7.1)]*.

Food: A crossover study in 26 healthy adult 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.

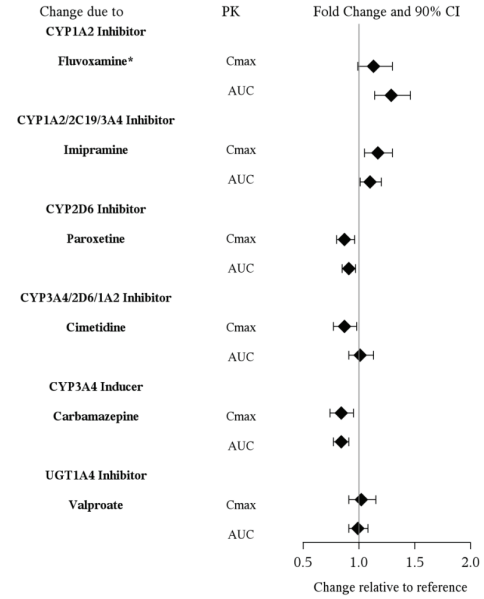
In clinical trials establishing the efficacy and safety of SAPHRIS, patients were instructed to avoid eating for 10 minutes following sublingual dosing. There were no other restrictions with regard to the timing of meals in these trials *[see Dosage and Administration (2.1) and Patient Counseling Information (17)]*.

Water: In clinical trials establishing the efficacy and safety of SAPHRIS, patients were instructed to avoid drinking for 10 minutes following sublingual dosing. The effect of water administration following 10 mg sublingual SAPHRIS dosing was studied at different time points of 2, 5, 10, and 30 minutes in 15 healthy adult male subjects. The exposure of asenapine following administration of water 10 minutes after sublingual dosing was equivalent to that when water was administered 30 minutes after dosing. Reduced exposure to asenapine was observed following water administration at 2 minutes (19% decrease) and 5 minutes (10% decrease) *[see Dosage and Administration (2.1) and Patient Counseling Information (17)]*.

Drug Interaction Studies:

Effects of other drugs on the exposure of asenapine are summarized in Figure 1. In addition, a population pharmacokinetic analysis indicated that the concomitant administration of lithium had no effect on the pharmacokinetics of asenapine.

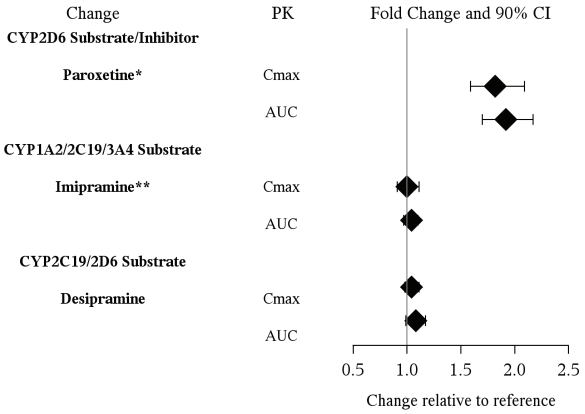
Figure 1: Effect of Other Drugs on Asenapine Pharmacokinetics



*: When a low dose of 25 mg twice daily fluvoxamine was co-administered with asenapine, a 29% increase in asenapine exposure was observed. Concomitant use of a therapeutic dose of fluvoxamine may cause greater increases in asenapine exposure.

The effects of asenapine on the pharmacokinetics of other co-administered drugs are summarized in Figure 2. Coadministration of paroxetine with SAPHRIS caused a two-fold increase in the maximum plasma concentrations and systemic exposure of paroxetine. Asenapine enhances the inhibitory effects of paroxetine on its own metabolism by CYP2D6.

Figure 2: Effect of Asenapine on Other Drug Pharmacokinetics



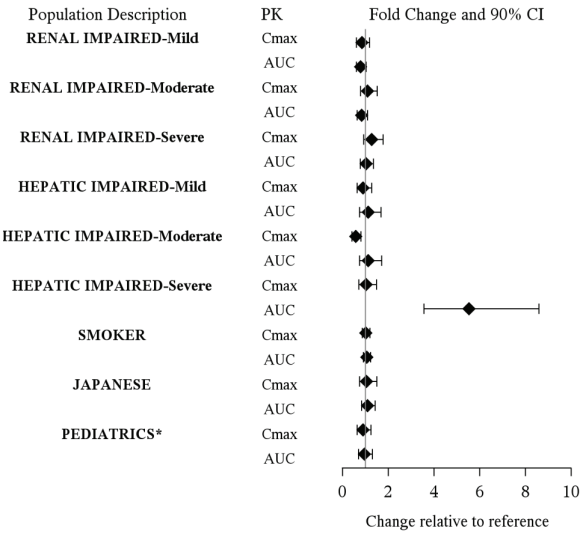
*: Asenapine may enhance the inhibitory effects of paroxetine on its own metabolism.

**: In vivo, Asenapine appears to be at most a weak inhibitor of CYP2D6. Following coadministration of dextromethorphan and SAPHRIS in healthy subjects, the ratio of dextrorphan/dextromethorphan (DX/DM) as a marker of CYP2D6 activity was measured. Indicative of CYP2D6 inhibition, treatment with SAPHRIS 5 mg twice daily decreased the DX/DM ratio to 0.43. In the same study, treatment with paroxetine 20 mg daily decreased the DX/DM ratio to 0.032. In a separate study, coadministration of a single 75 mg dose of imipramine with a single 5 mg dose of SAPHRIS did not affect the plasma concentrations of the metabolite desipramine (a CYP2D6 substrate).

Studies in Special Populations:

Exposures of asenapine in special populations are summarized in Figure 3. Additionally, based on population pharmacokinetic analysis, no effects of sex, race, BMI, and smoking status on asenapine exposure were observed. Exposure in elderly patients is 30-40% higher as compared to adults.

Figure 3: Effect of Intrinsic Factors on Asenapine Pharmacokinetics



*: Results are based on a cross-trial comparison.
The data shown for renal and hepatic impairment are relative to subjects with normal renal and hepatic function, respectively.
The data shown for smoker are relative to non-smoker.
The data shown for Japanese are relative to Caucasian.
The data shown for pediatrics are relative to adults.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: 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 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 5 times those in humans receiving the MRHD.

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.

Impairment of Fertility: Asenapine did not impair fertility in rats when tested at doses up to 11 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/m^2 basis.

14 CLINICAL STUDIES

Efficacy of SAPHRIS was established in the following trials:

- Two fixed-dose, short-term trials and one flexible-dose, maintenance trial in adult patients with schizophrenia as monotherapy *[see Clinical Studies (14.1)]*
- Two flexible-dose, short-term trials in adult patients and one fixed-dose, short-term trial in children (10 to 17 years) with manic or mixed episode associated with bipolar I disorder as monotherapy *[see Clinical Studies (14.2)]*
- One flexible-dose, short-term trial in adult patients with manic or mixed episode associated with bipolar I disorder as adjunctive treatment to lithium or valproate *[see Clinical Studies (14.2)]*

14.1 Schizophrenia

The efficacy of SAPHRIS in the treatment of schizophrenia in adults was evaluated in three fixed-dose, short-term (6 week), randomized, double-blind, placebo-controlled, and active-controlled (haloperidol, risperidone, and olanzapine) trials of adult patients who met DSM-IV criteria for schizophrenia and were having an acute exacerbation of their schizophrenic illness. In two of the three trials SAPHRIS demonstrated superior efficacy to placebo. In a third trial, SAPHRIS could not be distinguished from placebo; however, an active control in that trial was superior to placebo.

In the two positive trials for SAPHRIS**,** the primary efficacy rating scale was the Positive and Negative Syndrome Scale (PANSS). The PANSS is a 30 item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); total PANSS scores range from 30 to 210. The primary endpoint was change from baseline to endpoint on the PANSS total score. The results of the SAPHRIS trials in schizophrenia follow:

In trial 1, a 6-week trial (n=174), comparing SAPHRIS (5 mg twice daily) to placebo, SAPHRIS 5 mg twice daily was statistically superior to placebo on the PANSS total score (Trial 1 in Table 13).

In trial 2, a 6-week trial (n=448), comparing two fixed doses of SAPHRIS (5 mg and 10 mg twice daily) to placebo, SAPHRIS 5 mg twice daily was statistically superior to placebo on the PANSS total score. SAPHRIS 10 mg twice daily showed no added benefit compared to 5 mg twice daily and was not significantly different from placebo (Trial 2 in Table 13).

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, sex or race.

Table 13: Adult Schizophrenia Trials Establishing Efficacy

Trial Number	Treatment Group	Primary Efficacy Measure: PANSS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Trial 1	SAPHRIS 5 mg* twice daily	96.5 (16.4)	-14.4 (2.6)	-9.7 (-17.6, -1.8)
	Placebo	92.4 (14.9)	-4.6 (2.5)	--
Trial 2	SAPHRIS 5 mg* twice daily	89.2 (12.0)	-16.2 (1.7)	-5.5 (-10.7, -0.2)
	SAPHRIS 10 mg twice daily	89.1 (12.9)	-14.9 (1.7)	-4.1 (-9.4, 1.2)
	Placebo	88.9 (11.7)	-10.7 (1.6)	--

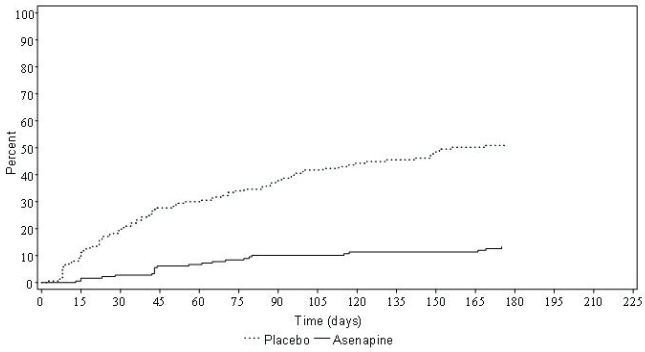
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiple comparisons.

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

* Doses that are demonstrated to be effective.

Maintenance of efficacy has been demonstrated in a placebo-controlled, double-blind, multicenter, flexible dose (5 mg or 10 mg twice daily based on tolerability) clinical trial with a randomized withdrawal design (Study 3). All patients were initially administered 5 mg twice daily for 1 week and then titrated up to 10 mg twice daily. A total of 700 patients entered open-label treatment with SAPHRIS for a period of 26 weeks. Of these, a total of 386 patients who met pre-specified criteria for continued stability (mean length of stabilization was 22 weeks) were randomized to a double-blind, placebo-controlled, randomized withdrawal phase. SAPHRIS was statistically superior to placebo in time to relapse or impending relapse defined as increase in PANSS ≥20% from baseline and a Clinical Global Impression–Severity of Illness (CGI-S) score ≥4 (at least 2 days within 1 week) or PANSS score ≥5 on "hostility" or "uncooperativeness" items and CGI-S score ≥4 (≥2 days within a week), or PANSS score ≥5 on any two of the following items: "unusual thought content," "conceptual disorganization," or "hallucinatory behavior" items, and CGI-S score ≥4 (≥2 days within 1 week) or investigator judgment of worsening symptoms or increased risk of violence to self (including suicide) or other persons. The Kaplan-Meier curves of the time to relapse or impending relapse during the double-blind, placebo-controlled, randomized withdrawal phase of this trial for SAPHRIS and placebo are shown in Figure 4.

Figure 4: Kaplan-Meier Estimation of Percent Relapse/Impending Relapse for SAPHRIS and Placebo



Time(days) represents the number of days from randomization to the first date of achieving relapse/impending relapse status.
The product limit estimators are based on the Kaplan-Meier distribution with censoring at last double-blind dose date.

14.2 Bipolar Disorder

Monotherapy

Adults: The efficacy of SAPHRIS in the treatment of acute mania was established in two similarly designed 3-week, randomized, double-blind, placebo-controlled, and active-controlled (olanzapine) trials of adult patients who met DSM-IV criteria for Bipolar I Disorder with an acute manic or mixed episode with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (YMRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). Patients were also assessed on the Clinical Global Impression – Bipolar (CGI-BP) scale. In both trials, all patients randomized to SAPHRIS were initially administered 10 mg twice daily, and the dose could be adjusted within the dose range of 5 to 10 mg twice daily from Day 2 onward based on efficacy and tolerability. Ninety percent of patients remained on the 10 mg twice daily dose. SAPHRIS was statistically superior to placebo on the YMRS total score and the CGI-BP Severity of Illness score (mania) in both studies (Trials 1 and 2 in Table 14).

An examination of subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, sex, or race.

Pediatric patients: The efficacy of SAPHRIS in the treatment of acute mania was established in a single, 3-week, placebo-controlled, double-blind trial of 403 pediatric patients 10 to 17 years of age, of whom 302 patients received SAPHRIS at fixed doses of 2.5 mg, 5 mg and 10 mg twice daily. All patients were started on 2.5 mg twice daily. For those assigned to 5 mg twice daily, the dose was increased to 5 mg twice daily after 3 days. For those assigned to 10 mg twice daily, the dose was increased from 2.5 to 5 mg twice daily after 3 days, and then to 10 mg twice daily after 3 additional days.

SAPHRIS was statistically superior to placebo in improving YMRS total score and the CGI-BP Severity of Illness score (overall) as measured by the change from baseline to week 3 (Trial 3 Pediatric in Table 14). An examination of subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, sex, and race.

Adjunctive Therapy: The efficacy of SAPHRIS as an adjunctive therapy in acute mania was established in a 12-week, placebo-controlled trial with a 3-week primary efficacy endpoint involving 326 adult patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially responsive to lithium or valproate monotherapy after at least 2 weeks of treatment. All patients randomized to SAPHRIS were initially administered 5 mg twice daily, and the dose could be adjusted within the dose range of 5 to 10 mg twice daily from Day 2 onward based on efficacy and tolerability. SAPHRIS was statistically superior to placebo in the reduction of manic symptoms

(measured by the YMRS total score) as an adjunctive therapy to lithium or valproate monotherapy at Week 3 (Trial 4 Adjunctive in Table 14).

Table 14: Bipolar 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)
Trial 1	SAPHRIS 5-10 mg* twice daily	29.4 (6.7)	-11.5 (0.8)	-3.7 (-6.6, -0.7)
	Placebo	28.3 (6.3)	-7.8 (1.1)	--
Trial 2	SAPHRIS 5-10 mg* twice daily	28.3 (5.5)	-10.8 (0.8)	-5.3 (-8.0, -2.5)
	Placebo	29.0 (6.1)	-5.5 (1.0)	--
Trial 3 (Pediatric 10 to17 years)	SAPHRIS 2.5 mg* twice daily	29.5 (5.7)	-12.8 (0.8)	-3.2 (-5.6, -0.8)
	SAPHRIS 5 mg* twice daily	30.4 (5.9)	-14.9 (0.8)	-5.3 (-7.7, -2.9)
	SAPHRIS 10 mg* twice daily	30.1 (5.7)	-15.8 (0.9)	-6.2 (-8.6, -3.8)
	Placebo	30.1 (5.7)	- 9.6 (0.9)	--
Trial 4 (Adjunctive)	SAPHRIS 5-10 mg* twice daily + lithium/Valproate	28.0 (5.6)	-10.3 (0.8)	-2.4 (-4.4, -0.3)
	Lithium/Valproate	28.2 (5.8)	-7.9 (0.8)	--

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.

16 HOW SUPPLIED/STORAGE AND HANDLING

SAPHRIS (asenapine) sublingual tablets are supplied as:

2.5 mg Tablets, black cherry flavor

Round, white to off-white sublingual tablets, with a hexagon on one side.

Child-resistant packaging

Box of 60	6 blisters with 10 tablets	NDC 0456-2402-60

Hospital Unit Dose

Box of 100	10 blisters with 10 tablets	NDC 0456-2402-63

5 mg Tablets, black cherry flavor

Round, white to off-white sublingual tablets, with "5" on one side within a circle.

Child-resistant packaging

Box of 60	6 blisters with 10 tablets	NDC 0456-2405-60

Hospital Unit Dose

Box of 100	10 blisters with 10 tablets	NDC 0456-2405-63

10 mg Tablets, black cherry flavor

Round, white to off-white sublingual tablets, with "10" on one side within a circle.

Child-resistant packaging

Box of 60	6 blisters with 10 tablets	NDC 0456-2410-60

Hospital Unit Dose

Box of 100	10 blisters with 10 tablets	NDC 0456-2410-63

Storage

Store at 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Dosage and Administration

Counsel patients on proper sublingual administration of SAPHRIS and advise them to read the FDA-approved patient labeling (Instructions for Use). When initiating treatment with SAPHRIS, provide dosage escalation instructions *[see Dosage and Administration (2)]*.

Hypersensitivity Reactions

Counsel patients on the signs and symptoms of a serious allergic reaction (e.g., difficulty breathing, itching, swelling of the face, tongue or throat, feeling lightheaded etc.) and to seek immediate emergency assistance if they develop any of these signs and symptoms *[see Contraindications (4), Warnings and Precautions (5.6) and Adverse Reactions (6)]*.

Application Site Reactions

Inform patients that application site reactions, primarily in the sublingual area, including oral ulcers, blisters, peeling/sloughing and inflammation have been reported. Instruct patients to monitor for these reactions *[see Adverse Reactions (6.2)]*. Inform patients that numbness or tingling of the mouth or throat may occur directly after administration of SAPHRIS and usually resolves within 1 hour *[see Adverse Reactions (6.1)]*.

Neuroleptic Malignant Syndrome

Counsel patients about a potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) that has been reported in association with administration of antipsychotic drugs. Patients should contact their health care provider or report to the emergency room if they experience the following signs and symptoms of NMS, including hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.3)]*.

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their health care provider if these abnormal movements occur *[see Warnings and Precautions (5.4)]*.

Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain)

Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia (high blood sugar) and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.5)]*.

Orthostatic Hypotension

Educate patients about the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing) especially early in treatment, and also at times of re-initiating treatment or increases in dose *[see Warnings and Precautions (5.7)]*.

Leukopenia/Neutropenia

Advise patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia they should have their CBC monitored while taking SAPHRIS *[see Warnings and Precautions (5.8)]*.

Interference with Cognitive and Motor Performance

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that SAPHRIS therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

Heat Exposure and Dehydration

Counsel patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.13)]*.

Concomitant Medications

Advise patients to inform their health care provider if they are taking, or plan to take, any prescription or over-the-counter medications since there is a potential for interactions *[see Drug Interactions (7.1)]*.

Pregnancy

Advise patients that SAPHRIS may cause fetal harm as well as extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients to notify their healthcare provider with a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SAPHRIS during pregnancy *[see Use in Specific Populations (8.1)]*.

Manufactured by: Catalent UK Swindon Zydis Ltd., Blagrove, Swindon, Wiltshire, SN5 8RU, UK

Distributed by:
Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, LLC
Cincinnati, OH 45209

U.S. Patent Nos. 5,763,476 and 7,741,358.

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SPH29296-P-3/2015

INSTRUCTIONS FOR USE

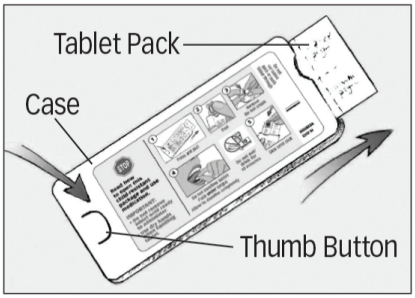
SAPHRIS® (asenapine)
sublingual tablets

Read these Instructions for Use before you start using SAPHRIS and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or your treatment.

IMPORTANT:

- **For sublingual (under your tongue) use only**
- **Do not remove tablet until ready to administer.**
- **Use dry hands when handling tablet.**

Your SAPHRIS tablets



Directions for Taking your SAPHRIS Tablets:

Step 1. Firmly press and hold thumb button, then pull out the tablet pack (see Figure A). **Do not push tablet through the tablet pack. Do not cut or tear the tablet pack.**

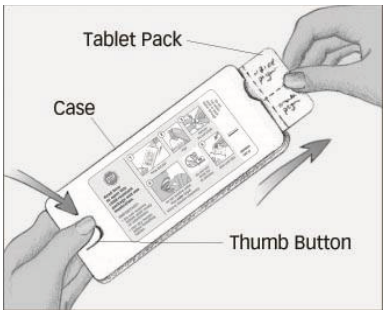


Figure A

Step 2. Peel back the colored tab (see Figure B).

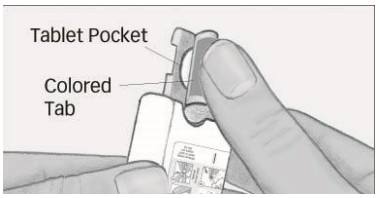


Figure B

Step 3. Gently remove the tablet (see Figure C). **Do not split, cut or crush the tablet.**

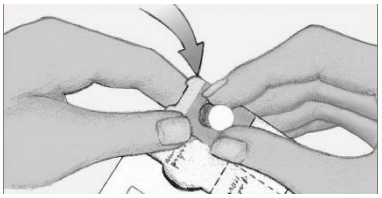


Figure C

Step 4. Place the **whole** tablet **under** tongue and allow it to dissolve completely (see Figure D).

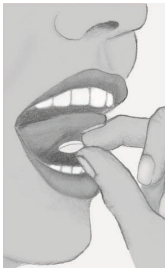


Figure D

Do not chew or swallow the tablet.
Do not eat or drink for 10 minutes (See Figure E).

Figure E

Step 5. Slide the tablet pack back into case until it clicks (see Figure F).

Figure F

Storing SAPHRIS tablets:
Store SAPHRIS tablets at room temperature between 68°F to 77°F (20°C to 25°C).

These Instructions for Use have been approved by the U.S. Food and Drug Administration.

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