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.
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)

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**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**

**DOSE AND ADMINISTRATION**

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

**DOSE 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)

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**RECENT MAJOR CHANGES**

Boxed Warning: 10/2014
Indications and Usage: 03/2015
Dosage and Administration: 03/2015
Contraindications: 04/2015
Warnings and Precautions: 03/2015

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**DRUG INTERACTIONS**

- Anthypertensive Drugs: SAPHRIS may cause hypotension. (5.7, 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
1 INDICATIONS AND USAGE
SAPHRIS is indicated for:
- Schizophrenia [see Clinical Studies (14.1)]
- Acute treatment of mania 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 swallowing [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 trials [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 aged 16 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 5 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 dyskinesia 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 "S" on one side with a circle in 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 (12.2)].
- 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 16 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in 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, sepsis) and untreated or inadequately treated extrapyramidal symptoms and signs (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. In patients who do require chronic treatment with antipsychotic drugs, it is important to carefully choose an antipsychotic drug with a recognized acceptable risk-benefit profile and titrate up slowly, recognizing the dose-related nature of the syndrome. 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 risk of developing tardive dyskinesia is greater in elderly patients, tardive dyskinesia can occur in any age group administered antipsychotic drugs. When a patient requires antipsychotic 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.

5.5 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, 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. The patient 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.

- 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.
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 1: Changes in Fasting Glucose in Adult Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Saphris 5 mg twice daily</th>
<th>Saphris 10 mg twice daily</th>
<th>Saphris 5 or 10 mg twice daily</th>
<th>Placebo</th>
<th>Saphris 2.5 mg twice daily</th>
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</thead>
<tbody>
<tr>
<td>Mean change from baseline (mg/dL)</td>
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<td>Normal to Low (&lt;100 mg/dL)</td>
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<tr>
<td>Total cholesterol</td>
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### TABLE 2: Changes in Fasting Glucose in Pediatric Subjects

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<td>HDL (mg/dL)</td>
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### TABLE 3: Changes in Lipids in Adult Patients

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### TABLE 4: Changes in Fasting Lipids in Pediatric Subjects

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### TABLE 5: Changes in Body Weight in Adult Patients from Baseline

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<td>-0.1</td>
<td>-0.1</td>
<td>-0.1</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

**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).]

Pediatric Patients: Pooled data on mean changes in body weight and the proportion of subjects meeting the weight gain criterion of ≥7% of body weight from the short-term, placebo-controlled schizophrenia and bipolar mania trials are presented in Table 5.
The use of SAPHRIS should be avoided in combination with other drugs known to prolong QTc including Class 1A antihyrrythmics (e.g., quinidine, procainamide) or Class 3 antihyrrythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and antibiotics (e.g., gentamicin, moxifloxacin). SAPHRIS should also be avoided in patients with a history of cardiac arrhythmias and in other circumstances that may increase the risk of occurrence of torsades de pointes (TDP) or sudden death in association with the use of drugs that prolong the QTc-interval, including bradycardia: hypokalemia or hypomagnesemia; a presence of congenital prolongation of the QT interval.

5.10 Hyperprolactinemia

Like other drugs that antagonize dopamine D2 receptors, SAPHRIS can elevate prolactin levels, and the elevation can persist during chronic administration. Hyperprolactinemia may suppress serum testosterone levels in pre/postmenopausal women and men, respectively. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male subjects. 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. SAPHRIS adult clinical trials also revealed no 2 events related to abnormal prolactin levels were 0.4% versus 0.0% for placebo. In a 3-week, bipolar manic patient 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 1% for patients treated with placebo [See Adverse Reactions (6.1)].

Tissue culture experiments indicate that approximately one-third of human breast cancers are progesterone 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 trials 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

In clinical trials, 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, 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 13% (41/324) of patients on SAPHRIS 2.5 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% (385/2033) 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), 63% (52/82), and 49% (48/99), 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

SAPHRIS is not known to adversely affect core body temperature in healthy young adults. In 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 or hyperpyrexia) was low (≤1%).

Appropriate care is advised when prescribing SAPHRIS for patients who will be experiencing environmental 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% (0/578, 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.

Esophageal dysmotility and aspiration may be associated with increased 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)].
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 Comorbid 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, 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 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.

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 8.

<table>
<thead>
<tr>
<th>System Organ Class/ Preferred Term</th>
<th>Placebo N=378</th>
<th>SAPHRIS 5 mg twice daily N=274</th>
<th>SAPHRIS 10 mg twice daily N=208</th>
<th>All SAPHRIS5 mg or 10 mg N=572</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Oral hypoesthesia</td>
<td>1</td>
<td>6</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Salivary hypersalivation</td>
<td>0</td>
<td>&lt;1</td>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Stomatoh discomfort</td>
<td>1</td>
<td>&lt;1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Irritability</td>
<td>&lt;1</td>
<td>2</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Metabolism disorders</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Increased weight</td>
<td>≤1</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cognitive disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased appetite</td>
<td>&lt;1</td>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>3</td>
<td>4</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Extrapyramidal symptoms (excluding akathisia)</td>
<td>7</td>
<td>9</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Somnolence</td>
<td>7</td>
<td>15</td>
<td>13</td>
<td>13</td>
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<tr>
<td>Psychiatric disorders</td>
<td>13</td>
<td>16</td>
<td>15</td>
<td>15</td>
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<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

* Akathisia includes: akathisia and hyperkinesia.
† Extrapyramidal symptoms included dystonia, oculogyration, dyskinesia, tardive dyskinesia, muscle rigidity, parkinsonism, tremor, and extrapyramidal disorder (excluding akathisia).
‡ Also includes the Flexible-dose trial (N=90).
§ See Warnings and Precautions (5.15).
\[see Warnings and Precautions (5.16)\]
\[see Warnings and Precautions (5.17)\]
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

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

* 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 1% 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 at Greater Incidence Than in the Placebo Group in a 3-Week Bipolar Mania Trial

<table>
<thead>
<tr>
<th>System Organ Class/ AE Preferred Term</th>
<th>Placebo N=101 %</th>
<th>SAPHRIS 2.5 mg twice daily N=104 %</th>
<th>SAPHRIS 5 mg twice daily N=99 %</th>
<th>SAPHRIS 10 mg twice daily N=99 %</th>
<th>All SAPHRIS N=302 %</th>
</tr>
</thead>
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<tr>
<td>Cardiac Disorders</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Tachycardia†</td>
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<td>3</td>
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<td>Cardiomyopathy</td>
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<tr>
<td>Gastrointestinal Disorders</td>
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<td></td>
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<tr>
<td>Oral parasthesia†</td>
<td>4</td>
<td>25</td>
<td>25</td>
<td>30</td>
<td>27</td>
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<td>Nausea</td>
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<tr>
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<td>4</td>
<td>4</td>
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<td>4</td>
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<tr>
<td>Abdominal pain†</td>
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<td>8</td>
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<td>Nervous System Disorders</td>
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<td>Somnolence‡</td>
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<td>11</td>
<td>5</td>
<td>9</td>
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<td>0</td>
<td>10</td>
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<td>7</td>
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<td>Insomnia</td>
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<td>3</td>
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<tr>
<td>Suicidal ideation</td>
<td>1</td>
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<td>1</td>
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</tr>
<tr>
<td>Mania</td>
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<td>0</td>
<td>2</td>
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<tr>
<td>Reproductive System and Breast Disorders</td>
<td></td>
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<tr>
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<td>1</td>
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<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
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<tr>
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<td>1</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
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<td></td>
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<td></td>
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</tr>
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<td>Rash</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

1 Includes the preferred terms tachycardia and heart rate increased.
2 Includes the preferred terms oral hypothyroidism, oral parathyroidism, 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).

Adjuvative 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 adjuvative 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 (Adjuvative) 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 adjuvantive therapy at 3 weeks, a time when most of the patients were still participating in the trial, are shown in Table 11.
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 mg/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 galactorrhea or dysmenorrhea in this trial.

Other Adverse Reactions Observed During the Premarking 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); those occurring in 1/1000 to 1/100 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: dry, swollen tongue
General disorders: rare: disosmycotic drug reaction
Hypersensitivity disorders: infrequent: dysarthria
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/slooughing, and inflammation.

Choking has been reported by patients, some of whom may have also experienced oropharyngeal muscular dysfunction or hypophonia.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Drug Interactions with SAPHRIS

<table>
<thead>
<tr>
<th>Concomitant Drug Name or Drug Class</th>
<th>Clinical Rationale</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive Drugs</td>
<td>Because of its α₁-adrenergic antagonism without potential inducing hypotension, SAPHRIS may enhance the effects of certain antihypertensive agents [see Warnings and Precautions (5)].</td>
<td>Monitor blood pressure and adjust dosage of antihypertensive drug accordingly.</td>
</tr>
<tr>
<td>Strong CYP1A2 Inhibitors (e.g., Fluvoxamine)</td>
<td>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.</td>
<td>Dosage reduction for SAPHRIS based on clinical response may be necessary.</td>
</tr>
<tr>
<td>CYP2D6 substrates and inhibitors (e.g., paroxetine)</td>
<td>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)].</td>
<td>Reduce paroxetine dose by half when paroxetine is used in combination with SAPHRIS.</td>
</tr>
</tbody>
</table>
7.2 Drugs Having No Clinically Important Interactions with SAPHRIS
No dosage adjustment of SAPHRIS is necessary when administered concomitantly with prochlorperazine (Table 12 in Drug Interactions (7.1) for prochlorperazine dosage adjustment), imipramine, cimetidine, valproate, 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 acid 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.orgclinical-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. Asenapine has not been studied in pregnant women. There are no available human data informing the drug's 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 at intravenous doses of asenapine to rats and rabbits during organogenesis at doses of 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, hypotonia, hyperactivity, 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/m2 basis. Plasma levels of asenapine were measured in the rabbit study, and 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/m2 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 mg 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/m2 basis) resulted in significant reduction in body weight gain in 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. Neurobehavioural 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 animals in pattern as late as day 50 following the completion of the treatment period (retesting). These data indicate that No Observed Adverse Effect Level (NOAEL) for the juvenile animal toxicity of asenapine could not be determined. There were no treatment-related changes 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 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. SAPIRIS 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 Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE

Human Experience: In adult pre-marketing clinical studies involving more than 3350 patients and/or healthy subjects, accidental or intentional acute overdose 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 Overdose: There is no specific antidote to SAPHRIS. The possibility of multiple drug involvement should be considered. An electrocardiogram should be obtained and management of an 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 overdose (1-800-222-1222).

Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agent (e.g., dopamine and norepinephrine) and 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 (3aR,12bS)-6-Chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-indeno[2,3,6:5,4]pyrrole[4,5-c]pyrrole(2,3-2-butenedione (1.1). Its molecular formula is C23H22ClNO3CH2OH 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, sucrose, 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 5-HT6, 5-HT7, and D2 receptors.

12.2 Pharmacodynamics

Asenapine exhibits high affinity for serotonin 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C, 5-HT6, 5-HT7, and D2 receptors (Ki values of 2.5, 2.7, 0.07, 0.18, 0.03, 1.6, 0.25, and 0.11 nM, respectively). 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 peak plasma concentrations and systemic exposure of paroxetine. Asenapine enhances the inhibitory effects of paroxetine on its own metabolism by CYP2D6.

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 peak plasma concentrations and systemic exposure of paroxetine. Asenapine enhances the inhibitory effects of paroxetine on its own metabolism by CYP2D6.

Distribution:

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

Metabolism and Elimination:

Direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isozymes (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 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.

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siveness on the basis of age, sex or race.

In the two positive trials for SAP HRIS, an examination of 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

<table>
<thead>
<tr>
<th>Trial Number</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: PANSS Total Score</th>
<th>Change from Baseline</th>
<th>Placebo-subtracted Differencea (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>SAPHRIS 5 mg* twice daily</td>
<td>96.5 (16.4)</td>
<td>-14.4 (2.6)</td>
<td>-9.7 (-17.6, -1.8)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>92.4 (14.9)</td>
<td>-4.6 (2.5)</td>
<td>--</td>
</tr>
<tr>
<td>Trial 2</td>
<td>SAPHRIS 5 mg* twice daily</td>
<td>89.1 (12.9)</td>
<td>-14.9 (1.7)</td>
<td>-4.1 (-9.4, 1.2)</td>
</tr>
<tr>
<td></td>
<td>SAPHRIS 10 mg twice daily</td>
<td>88.9 (11.7)</td>
<td>-10.7 (1.6)</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Placebo: standard deviation; ES: 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 586 patients who met pre-specified criteria for continued stabilization (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 ≥3 on “hostility” or “uncooperativeness” items and CGI-S score ≥4 (≥2 days within a week), or PANSS score ≥5 on any of the following items: “unusual thought content,” “conceptual disorganization,” or “hallucinatory behavior” items, and CGI-S score ≥4 (≥2 days within a week) or investigator judgment of worsening symptoms or increased risk of violence to self (including suicide) or others. 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.

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 vitro 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/m² 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 II 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 14: Bipolar Trials**

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: YMRS Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Baseline Score (SD)</td>
<td>LS Mean Change from Baseline (SE)</td>
</tr>
<tr>
<td>Trial 1</td>
<td>SAPHRIS 5-10 mg* twice daily Placebo</td>
<td>29.4 (6.7)</td>
</tr>
<tr>
<td></td>
<td>SAPHRIS 5-10 mg* twice daily Placebo</td>
<td>28.3 (6.3)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>SAPHRIS 5-10 mg* twice daily Placebo</td>
<td>28.3 (5.5)</td>
</tr>
<tr>
<td>(Pediatric 10 to 17 years)</td>
<td>SAPHRIS 2.5 mg* twice daily Placebo</td>
<td>29.0 (6.1)</td>
</tr>
<tr>
<td>Trial 3</td>
<td>SAPHRIS 5-10 mg* twice daily Placebo</td>
<td>29.3 (5.7)</td>
</tr>
<tr>
<td></td>
<td>SAPHRIS 5-10 mg* twice daily Placebo</td>
<td>30.4 (5.9)</td>
</tr>
<tr>
<td></td>
<td>SAPHRIS 10 mg* twice daily Placebo</td>
<td>30.1 (5.7)</td>
</tr>
<tr>
<td>Trial 4</td>
<td>SAPHRIS 5-10 mg* twice daily lithium/Valproate Placebo</td>
<td>28.0 (5.6)</td>
</tr>
<tr>
<td></td>
<td>SAPHRIS 5-10 mg* twice daily lithium/Valproate Placebo</td>
<td>30.1 (5.7)</td>
</tr>
</tbody>
</table>

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

**Hypersecretion 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 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 increase 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 healthcare 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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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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