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A Treatment for Schizophrenia in Adults

Narrator:

You're listening to ReachMD. Welcome to this week's industry feature sponsored by Actavis, the marketer and distributor of SAPHRIS (asenapine) sublingual tablets. See the full Prescribing Information, including Boxed Warning, for SAPHRIS at www.SAPHRISHCP.com.The following program is intended for U.S. healthcare professionals only. Your host is Dr. Matt Birnholz, and, your guest is Dr. Roger McIntyre, who is a paid consultant for Actavis.

Dr. Birnholz:

In this presentation, we will focus on the clinical profile of SAPHRIS for the acute and maintenance treatment of schizophrenia in adults. Included in this discussion will be a review of the safety data for SAPHRIS from the Adult Schizophrenia Clinical Trials. And, we will also review Important Safety Information for SAPHRIS.

I am your host, Dr. Matt Birnholz, and joining me today is Dr. Roger McIntyre. Dr. McIntyre is Professor of Psychiatry and Pharmacology at the University of Toronto and Head of the Mood Disorders Psychopharmacology Unit at the University Health Network.

Dr. McIntyre, welcome to ReachMD.

Dr. McIntyre:

Pleasure being here.

Dr. Birnholz:

Before we discuss the clinical profile for SAPHRIS, let's review the boxed warning and contraindications for SAPHRIS.

Dr. McIntyre:

Yes, the boxed warning for SAPHRIS is regarding an increased risk of death in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs. We want to emphasize that SAPHRIS is not approved for the treatment of patients who have dementia-related psychosis. In addition, SAPHRIS is contraindicated in patients with severe hepatic impairment, that is, Child-Pugh C, or in patients with known hypersensitivity to SAPHRIS or any of its formulation components. Hypersensitivity reactions, including anaphylaxis and angioedema, have been observed.

We will discuss additional Important Safety Information for SAPHRIS during this program.

Dr. Birnholz:

Dr. McIntyre, you are a recognized expert on mental health disorders, could you perhaps talk about SAPHRIS's indication in schizophrenia?

Dr. McIntyre:

Sure. SAPHRIS is indicated for the treatment of schizophrenia in adults, based on 3 acute short-term trials, as well as a long-term maintenance of effect trial. So for the acute trials, there were three double-blind, randomized, placebo- and active-controlled, fixed-dose trials in which the adults with acute exacerbation of their schizophrenic illness were initially hospitalized and treated for 6 weeks. In these trials, the primary efficacy rating scale was the Positive and Negative Syndrome Scale, or PANSS, which measures the 7 positive symptoms, the 7 negative symptoms, and 16 cognitive or general psychopathology symptoms of schizophrenia. It is important to note

that the efficacy of SAPHRIS was based on the PANSS total score, and not on any individual component of the scale. In 2 of the 3 trials, SAPHRIS met its primary efficacy endpoint and was statistically superior to placebo.

In Trial 1, a 6-week trial, comparing SAPHRIS to placebo, SAPHRIS 5 mg twice daily, or BID, was statistically superior to placebo on the PANSS total score. The mean change from baseline to week 6 in PANSS total score for the patients on SAPHRIS 5 mg twice daily was a decrease of 14.4 versus a decrease of 4.6 for placebo. And, in the second trial, you see similar results: a decrease from baseline of 16.2 for SAPHRIS versus a decrease of 10.7 for placebo.

In the third , short-term, 6-week, multicenter, randomized, double-blind, placebo- and active-controlled trial in adults, which included both 5 mg and 10 mg BID SAPHRIS arms, SAPHRIS could not be statistically distinguished from placebo; however, the active control in the trial was superior to placebo. This trial was considered a negative trial because the control, which was used for assay sensitivity, differentiated from placebo.

In the first trial, SAPHRIS was administered at 5 mg twice daily, or BID; in the second and third trials, SAPHRIS was administered at 5 mg BID or 10 mg BID. In general, 10 mg BID did not show an added benefit compared to 5 mg BID.

Dr. Birnholz:

What about the maintenance of effect trial?

Dr. McIntyre:

Regarding maintenance of effect, in the study, adult patients were administered open-label SAPHRIS 5 or 10 mg BID for up to 26 weeks, and then stable patients were randomized to a 26-week double-blind withdrawal period, where some patients stayed on SAPHRIS and other patients were treated with placebo. And the primary outcome was time to relapse or impending relapse. SAPHRIS was statistically superior to placebo in time to relapse or impending relapse. That is, the time to relapse or impending relapse was longer in the SAPHRIS group compared with the placebo group. The data showed a roughly four-fold difference in relapse or impending relapse rate between patients treated with SAPHRIS and those treated with placebo over the 26-week double-blind period. Patients should be periodically reassessed to determine the need for maintenance treatment.

Dr. Birnholz:

Thank you, Dr. McIntyre. I know you have taken a special interest in the area of metabolic issues, would you care to shed some light on SAPHRIS and its metabolic profile in adults?

Dr. McIntyre:

I'd be happy to, Dr. Matt. Now keep in mind, atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular or 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 change, each drug has its own specific risk profile.

So now let me start with weight. The total mean weighthe says the word weight a few times in this paragraph. See highlighted in pink] increase was on the order of about one kilogram, which corresponds to 2.2 pounds. During the 6-week Adult Schizophrenia Clinical Trials, the total mean weight increase was 1.1 kg for SAPHRIS 5 or 10 mg twice daily versus 0 kg for placebo. When we look at change in weight from baseline in the short-term trials, there are different ways you can present the data. One way is the clinically-significant threshold, which the FDA defines as 7% or greater increase in body weight. In the Adult Schizophrenia Clinical Trials, 4.9% of patients experienced a 7% or greater increase in weight with SAPHRIS 5 or 10 mg BID versus 1.6% with placebo.

We're interested in weight not only in the short-term but also long-term. The mean weight gain from baseline in the long-term, 52-week trial that included primarily patients with schizophrenia, was reported to be 0.9 kilograms. I'll round that off to about 2 pounds or so. In this study, about 14.7% of patients had at least a 7% increase in body weight at endpoint. Now you need to keep in mind that SAPHRIS has a warning related to weight gain. Increases in weight have been observed with SAPHRIS, and patients should have their weight monitored regularly.

Dr. Birnholz:

Now let's talk about metabolic changes as they relate to hyperglycemia.

Dr. McIntyre:

We looked at fasting glucose in both the short-term and long-term trials. In the short-term 6-week Adult Schizophrenia Trials, we found a mean increase from baseline of up to about 3.2 mg/dL in fasting glucose levels for SAPHRIS 5 or 10 mg BID and a decrease of 0.2 in

placebo-treated subjects.

In the 52-week long-term trial, the mean increase from baseline in fasting glucose was 2.4mg/dL. There was no placebo arm in this trial. You can also refer to the full Prescribing Information for SAPHRIS to learn about the proportion of patients with shifts from normal or borderline to high fasting glucose during the course of the trial.

As a reminder, SAPHRIS has a warning related to hyperglycemia and diabetes mellitus. Hyperglycemia, in some cases associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. Patients with risk factors for diabetes mellitus starting treatment with antipsychotics should undergo fasting blood glucose testing at the beginning of and during treatment. Monitor any patient treated with antipsychotics for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop these symptoms during treatment should undergo fasting blood glucose testing. In some cases, hyperglycemia resolved when the antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the antipsychotic drug.

Dr. Birnholz:

Now, what about metabolic changes as they relate to lipids?

Dr. McIntyre:

It is important to keep in mind that undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. In the 6-week short-term, placebo-controlled Adult Schizophrenia Trials, placebo-treated patients had a mean decrease in total cholesterol from baseline of 2.2 mg/dL. The mean change from baseline in total cholesterol with SAPHRIS 5 or 10 mg BID was an increase of 0.4 mg/dL. Regarding fasting triglycerides, SAPHRIS 5 or 10 mg BID showed a mean increase of 3.8 mg/dL, while placebo-treated subjects had a mean decrease of 7.6 mg/dL. In the 52-week schizophrenia trial without placebo comparator, SAPHRIS-treated patients demonstrated mean reductions in total cholesterol and fasting triglycerides of 6 and 9.8 mg/dL, respectively, from baseline. As for mean changes in LDL and HDL during the 6-week, short-term studies, SAPHRIS-treated patients had an increase of 1.3 and 0.5 mg/dL, compared to placebo-treated patients who had a mean increase of 0.1 and 0.5 mg/dL, respectively. Similar to shifts in fasting glucose, shifts in lipid values from normal to abnormal can also be found in the Prescribing Information.

Dr. Birnholz:

Often we'll hear about patients who take antipsychotic medications bringing up prolactin-related side effects. Can you speak about this?

Dr. McIntyre:

We're always concerned about prolactin whenever we hear that an agent has affinity for the D_2 receptor, particularly, in the so-called tuberoinfundibular pathway. The effects on prolactin levels in the Short-Term Adult Schizophrenia Trials revealed that the mean decreases in prolactin levels were 6.5 ng/mL for SAPHRIS compared to 10.7 ng/mL for placebo. In the long-term, 52-week trial, the mean decrease in prolactin from baseline for SAPHRIS-treated patients was 26.9 ng/mL.

Please keep in mind that SAPHRIS has a warning relating to hyperprolactinemia. Like other drugs that antagonize dopamine D_2 receptors, SAPHRIS can elevate prolactin levels and the elevation can persist during chronic administration. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

Dr. Birnholz:

Thank you Dr. McIntyre for that review regarding SAPHRIS for the acute and maintenance treatment of schizophrenia in adults. Now, let's shift our discussion to the side effect profile of SAPHRIS from the Adult Schizophrenia Clinical Trials.

Dr. McIntyre:

Safety and side effects are always a consideration. Tolerability is also important because it is one of the main reasons why patients discontinue their medication. The most commonly observed adverse reactions—at an incidence of at least 5% and at least twice that of placebo—in the short-term placebo-controlled schizophrenia trials of SAPHRIS 5 or 10 mg twice daily in adults were somnolence 13% versus 7% placebo; oral hypoesthesia 5% versus 1% placebo; and akathisia 6% versus 3% placebo. The safety profile of SAPHRIS in the maintenance treatment of schizophrenia in adults was similar to that seen with acute treatment.

Akathisia includes both akathisia and hyperkinesia. And similarly, somnolence covers many symptoms as well. Somnolence includes: sedation, somnolence and hypersomnia. In clinical trials, somnolence was reported with SAPHRIS and was usually transient, with the highest incidence in the first week of treatment. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or a motor vehicle, until they are reasonably certain that SAPHRIS does not affect them

adversely.

Regarding the incidence of extrapyramidal symptoms, or EPS, excluding akathisia were 10% versus 7% with placebo. EPS-related events included dystonia, oculogyration, dyskinesia, tardive dyskinesia, muscle rigidity, parkinsonism, tremor, and extrapyramidal disorder, excluding akathisia. The incidence of akathisia was 6% versus 3% placebo.

Dr. Birnholz:

What were the discontinuation rates due to adverse reactions in the adult schizophrenia trials?

Dr. McIntyre:

The discontinuation rates due to adverse events in the adult schizophrenia trials were 9% for SAPHRIS versus 10% for placebo. In the adult schizophrenia studies, no drug-related adverse reactions leading to discontinuation occurred with SAPHRIS at an incidence of at least 1% and at least twice that of placebo.

Dr. Birnholz:

Dr. McIntyre, can you tell us about how SAPHRIS is administered?

Dr. McIntyre:

For schizophrenia in adults, 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 1 week. The safety of doses above 10 mg twice daily has not been evaluated in clinical studies. The dosing recommendations for SAPHRIS come from the clinical trials. There are no dosage adjustment recommendations based on age, gender, race, or renal impairment. However, remember that SAPHRIS is contraindicated in patients with severe hepatic impairment.

A few words on administration: SAPHRIS is for sublingual use only and the tablet should not be removed from the tablet pack until the patient is ready to take it. The tablet should always be handled with dry hands. Advise patients to follow the full administration instructions on the SAPHRIS tablet pack, and remind them not to split, cut, or crush the tablet. The whole SAPHRIS tablet should be placed under the tongue to dissolve completely; it should never be chewed or swallowed. The tablet will dissolve in saliva within seconds. Patients should not eat or drink for 10 minutes after taking a SAPHRIS tablet.

Dr. Birnholz:

Dr. McIntyre, thank you for the overview of the efficacy and safety profile of SAPHRIS from the Adult Schizophrenia Clinical Trials. Now, in addition to the Boxed Warning, contraindications, and metabolic changes discussed earlier, let's learn more Important Safety Information for SAPHRIS.

Narrator:

The following is additional Important Safety Information for SAPHRIS.

Cerebrovascular Adverse Events, Including Stroke: In clinical trials with antipsychotic drugs, elderly subjects with dementia had a higher incidence of cerebrovascular adverse reactions, including fatalities vs placebo. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome or NMS: NMS, a potentially fatal symptom complex, has been reported with antipsychotics, including SAPHRIS. NMS may cause hyperpyrexia, muscle rigidity, altered mental status, irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia. Additional signs may include elevated creatine phosphokinase, myoglobinuria or rhabdomyolysis, and acute renal failure. Management includes immediate discontinuation of antipsychotics and other drugs not essential to concurrent therapy, intensive symptomatic treatment and monitoring, and treatment of any concomitant serious medical problems.

Tardive Dyskinesia or TD: Risk of developing TD, a syndrome of potentially irreversible, involuntary dyskinetic movements, and the likelihood it will become irreversible may increase as the duration of treatment and total cumulative dose of antipsychotic drugs given to the patient increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribe SAPHRIS in a manner most likely to minimize TD. If signs and symptoms of TD appear, drug discontinuation should be considered.

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

Orthostatic Hypotension, Syncope, and Other Hemodynamic Effects: SAPHRIS may induce orthostatic hypotension and syncope. Use SAPHRIS with caution in patients with cardiovascular and/or cerebrovascular diseases, conditions which predispose to hypotension, and in the elderly. Use SAPHRIS cautiously with other drugs that can induce hypotension, bradycardia, or respiratory or central nervous system depression. Monitor orthostatic vital signs, and consider a dose reduction if hypotension occurs.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia and/or neutropenia have been reported with antipsychotics, including SAPHRIS. Agranulocytosis, including fatal cases, has been reported with other antipsychotics. Monitor complete blood count in patients with pre-existing low white blood cell count, WBC, and/or absolute neutrophil count or history of drug-induced leukopenia and/or neutropenia. Discontinue SAPHRIS at the first sign of a clinically-significant decline in WBC and in severely neutropenic patients.

QT Prolongation: In an adult QT study, SAPHRIS was associated with increases in the QTc interval from 2 to 5 milliseconds vs placebo. No SAPHRIS patients had QTc increases of ≥60 milliseconds or a QTc of ≥500 milliseconds. Avoid SAPHRIS in combination with other drugs known to prolong QTc interval, in patients with congenital prolongation of QT interval or a history of cardiac arrhythmias, and in circumstances that may increase occurrence of torsades de pointes and/or sudden death in association with the use of drugs that prolong QTc interval.

Seizures: Use SAPHRIS with caution in patients with history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment: Somnolence was reported with SAPHRIS. Caution patients about performing activities requiring mental alertness, for example, operating hazardous machinery or a motor vehicle.

Body Temperature Regulation: Appropriate care is advised when using SAPHRIS in patients who will experience conditions that increase body temperature, for example, exercising strenuously, extreme heat, concomitant anticholinergics, or dehydration.

Suicide: The possibility of suicide attempt is inherent in psychotic illnesses and bipolar disorder. Close supervision of high-risk patients should accompany drug therapy. Prescriptions should be written for the smallest quantity of tablets to reduce risk of overdose.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotics. Aspiration pneumonia is a common cause of morbidity and/or mortality in elderly patients, in particular, those with advanced Alzheimer's dementia. SAPHRIS should not be used in patients at risk for aspiration pneumonia.

Drug Interactions: Monitor blood pressure and adjust antihypertensive drugs when taken with SAPHRIS. Based on clinical response, SAPHRIS dose reduction may be necessary when used with strong CYP1A2 inhibitors, fluvoxamine. Reduce paroxetine, CYP2D6 substrate and inhibitor, dose by half when taken with SAPHRIS.

Pregnancy: Advise patients to notify their healthcare provider of a known or suspected pregnancy. SAPHRIS may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Based on animal data, SAPHRIS may cause fetal harm. The National Pregnancy Registry for Atypical Antipsychotics monitors pregnancy outcomes in women exposed to antipsychotics, including SAPHRIS, during pregnancy. For information, contact 1-866-961-2388.

Adverse Reactions: In adult schizophrenia clinical trials with SAPHRIS (5 and 10 mg BID) vs placebo, commonly observed adverse reactions (≥5% and at least twice the rate of placebo) were: akathisia (6% vs 3%), oral hypoesthesia (5% vs 1%), and somnolence (13% vs 7%).

And, in the Adult Bipolar I Adjunctive Trial, the most common adverse reactios for SAPHRIS were somnolence 22% vs 10% and oral hypesthesia 5% vs 0%. In the Pediatric Bipolar I Monotherapy Trial, the most commonly observed adverse reactions for SAPHRIS 2.5, 5 and 10 mg BID, were somnolence 49% vs 12%, dizziness 7% vs 3%, dysgeusia 6% vs 2%, oral paresthesia 27% vs 4%, nausea 6% vs 3%, increased appetite 8% vs 2%, fatigue 9% vs 5% and increased weight 3% vs 0%.

Postmarketing Experience: Application site reactions, primarily sublingual, have been reported, for example, oral ulcers, blisters, peeling, sloughing, and inflammation. Choking has been reported, sometimes associated with oropharyngeal muscular dysfunction or hypoesthesia.

Please also see the full Prescribing Information, including Boxed Warning for SAPHRIS at www.SAPHRISHCP.com

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