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A Treatment for Acute Manic or Mixed Episodes of Bipolar I Disorder 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 our discussion, we will focus on the clinical profile of SAPHRIS for the acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy, or adjunctive therapy with either lithium or valproate, in adults. Included in this discussion will also be a review of the safety data for SAPHRIS from the Bipolar I Disorder Clinical Trials in Adults. And, we will also review Important Safety Information for SAPHRIS.

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:

Thank you for having me.

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 category, 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:

As we mentioned earlier, our focus in today's discussion will be on the adult indication, but I recently heard that SAPHRIS was approved for an additional indication. Can you tell me more about it?

Dr. McIntyre:

Yes, I am excited to inform you that SAPHRIS was approved for the acute treatment of bipolar I manic, or mixed episodes, in pediatric patients ages 10-17 as monotherapy. The FDA approval of SAPHRIS is based on the results of a 3-week, placebo-controlled, monotherapy trial in 403 pediatric patients ages 10 –17, 302 of whom received SAPHRIS at fixed doses of either 2.5 mg, 5 mg, or 10 mg

twice daily, or BID.

This indication makes SAPHRIS the first atypical antipsychotic to be approved for use in pediatric patients with bipolar I disorder in the last five years. However the purpose of this program is to speak about the adult indication of bipolar I disorder, so let me tell you more about that.

Dr. Birnholz:

Thank you, Dr. McIntyre. Can you tell us about the Adult Bipolar I Disorder Clinical Trials for SAPHRIS?

Dr. McIntyre:

Be very happy to. I have to acknowledge that I was very privileged to be part of this development globally as a lead investigator and as a lead author. We conducted two double-blind, randomized, placebo- and active-controlled, flexible-dose studies with SAPHRIS in adult patients who had an acute manic or mixed episode with or without psychotic features. These were so-called parallel-group design studies that were three weeks in duration. And our principal arm of comparison was to placebo. These patients, in fact, started off with a dose of 10 mg BID of SAPHRIS. That could be adjusted from the dose range of 5 to 10 mg BID from Day 2 onward based on efficacy and tolerability. Most of the patients stayed on 10 mg BID.

As always is the case in these types of studies early in development, we had an active reference for assay sensitivity. Olanzapine was the active reference, but it wasn't a comparator; it was an active reference or an active control.

Dr. Birnholz:

And can you tell me what the results of the primary endpoint for SAPHRIS were in these trials?

Dr. McIntyre:

The primary instrument used was the Young Mania Rating Scale, or YMRS, which is a clinician-rated scale that measures 11 manic symptoms of bipolar I disorder. It is important to note that the efficacy of SAPHRIS was based on the YMRS total score, and not on any individual component of the scale.

And what we've found in both monotherapy studies, in fact, was a statistically significant effect at three weeks. In other words, at the pre-specified endpoint, we found that the overall reduction in the YMRS total score, that is, the change from baseline to Day 21, was statistically significantly greater with SAPHRIS-treated patients than it was in the placebo-treated patients. In Trial 1, a decrease of 5.5 from baseline in the placebo arm versus a decrease of 10.8 from baseline in the SAPHRIS 5 to 10 mg BID arm. And, in Trial 2, we see similar results: decrease of 7.8 in the placebo arm versus a decrease of 11.5 in the SAPHRIS 5 to 10 mg BID arm.

It's important to highlight that the types of statistics that we employed were based on an intent-to-treat population using the last observation carried forward method. Most clinicians are highly familiar with the fact that bipolar adults frequently require polypharmacy in order to achieve the symptomatic as well as functional therapeutic objectives. I think it's prudent for us to look not only at monotherapy trials, where we demonstrated replicated efficacy, but also at the adjunctive efficacy, safety, and tolerability of SAPHRIS.

Dr. Birnholz:

And there was an adjunctive trial, correct?

Dr. McIntyre:

Yes, we also did an adjunctive trial with SAPHRIS. This was, again, a placebo-controlled, parallel-group design trial. This was longer, 12 weeks in duration, but we did pre-specify Day 21 as our time point for primary efficacy assessment. The eligibility criteria in the adjunctive study were very similar to our monotherapy program; they, in fact, were adults with a manic or mixed episode of bipolar I disorder, with or without psychotic features.

What was different was that these individuals were on lithium or divalproex and had therapeutic levels of lithium or valproate, respectively, for a minimum of two weeks but were only partially responsive to these treatments. And if they continued to meet, as I said, the eligibility criteria, we would assign them to either placebo or to SAPHRIS, in addition to their ongoing lithium or divalproex therapy. In this adjunctive trial, instead of starting SAPHRIS at 10 mg BID, we started at 5 mg BID. And it could be flexibly dosed upwards to 10 mg BID based on efficacy and tolerability

And what we found was at the pre-specified efficacy endpoint, that is Day 21, the patients who received SAPHRIS added to lithium or divalproex had a statistically superior reduction of manic symptoms as measured by the YMRS total score, when compared to those patients who had received placebo added to lithium or divalproex. And, the mean change from baseline was -7.9 for placebo-treated

patients compared to -10.3 for the SAPHRIS-treated patients.

So taken together, what we actually saw was efficacy not only in the monotherapy program, but in the adjunctive program with SAPHRIS added to lithium or divalproex.

Dr. Birnholz:

So, obviously, efficacy is one side of the coin. What about the other side of the coin, that being its safety profile? In clinical practice most clinicians see many patients who discontinue their medication due to metabolic issues, such as hyperglycemia, dyslipidemia, and body weight gain. Would you care to shed some light on SAPHRIS and its metabolic profile in adults.

Dr. McIntyre:

I'd be happy to. 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 the metabolic changes, each drug has its own specific risk profile.

So now let me start with weight. And you know, you're absolutely right. As clinicians we often hear patients' concerns, valid indeed, about weight gain, and clinically-significant weight gain and associated metabolic changes are often the result of the medication.

In the 3-week, short-term, placebo-controlled, Bipolar Mania Monotherapy Trials in Adults, the placebo-treated patients had a mean increase from baseline of 0.2 kg and SAPHRIS-treated patients had a mean increase of 1.3 kg. When we look at change**s** in weight, there are different ways you can present the data. One way is the clinically-significant threshold, which **is,** the FDA defines as 7% or greater increase in body weight.

In the 3-week, Adult Bipolar I Clinical Trials, 5.8% of SAPHRIS 5 or 10 mg BID versus 0.5% of placebo-treated patients experienced a 7% or greater increase in body weight from baseline. 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:

And what about metabolic changes as they relate to hyperglycemia?

Dr. McIntyre:

We looked separately at fasting glucose in the 3-week Bipolar I Clinical Trials, and found a mean decrease of 0.6 mg/dL in fasting glucose in adults taking SAPHRIS 5 or 10 mg BID, as well as in those taking placebo.

So, 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 trials. As a reminder, SAPHRIS has a warning related to hyperglycemia and diabetes mellitus. Hyperglycemia, in some cases associated with ketoacidosis, hyperosmolar coma, or death, have 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:

Dr. McIntyre, what changes did you see in lipids, which are other types of metabolic concerns?

Dr. McIntyre:

It is important to keep in mind that undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Looking at lipids, we found an increase in total cholesterol of 1.1 mg/dL in the SAPHRIS-treated subjects, compared to a decrease of 1.5 mg/dL in the placebo-treated subjects. Regarding triglycerides, SAPHRIS-treated subjects had a decrease of 3.5 mg/dL, while placebo-treated subjects had a decrease of 17.9 mg/dL. As for mean changes in LDL and HDL, SAPHRIS-treated patients had an increase of 1.6 and 0.9 mg/dL respectively, compared to placebo-treated patients who had a mean increase of 1.9 for LDL and no change for HDL. 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 patients who take antipsychotic medications bringing up prolactin-related side effects. And with respect to prolactin, 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 Bipolar Mania Trials revealed that the mean increase in prolactin levels was 4.9 ng/mL for SAPHRIS compared to a decrease of 0.2 ng/mL for placebo.

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:

Now Dr. McIntyre, can you speak about the side effect profile of SAPHRIS from the acute bipolar mania clinical trials in adults?

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 Bipolar Mania Monotherapy Trials in Adults taking SAPHRIS—were somnolence at 24% versus placebo 6%; dizziness 11% versus placebo 3%; EPS other than akathisia 7% versus placebo 2%; and, increased weight at 5% versus placebo, less than 1%.

In the Bipolar Mania Adjunctive Trial, the most commonly observed adverse reactions in adults taking SAPHRIS were somnolence at 22% versus placebo 10%; and, oral hypoesthesia at 5% versus placebo 0%.

In two of the trials there was an increase in oral hypoesthesia, which is related to the sublingual formulation. Choking has been reported by patients, some of whom may have also experiencedoropharyngeal muscular dysfunction or hypoesthesia. When looking into the side effect data, it's important to understand what the terms include. For extrapyramidal symptoms, or EPS, it includes dystonia, blepharospasm, torticollis, dyskinesia, tardive dyskinesia, muscle rigidity, Parkinson's, gait disturbance, masked facies, and tremor—a whole range of symptoms are included under the term of EPS other than akathisia.

Akathisia was studied separately from EPS, and includes the terms akathisia and hyperkinesia, and similarly, somnolence covers many symptoms as well. Somnolence includes the terms sedation, somnolence, and hypersomnia. In clinical trials, somnolence was reported with SAPHRIS and was usually transient, with the highest incidence seen 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.

Dr. Birnholz:

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

Dr. McIntyre:

The SAPHRIS discontinuation rates due to adverse events were 10% versus 6% for placebo in the monotherapy trials and 16% versus 11% for placebo in the Adjunctive Bipolar I Trial. Now let's look into more detailed reasons for discontinuations due to adverse events. In the Monotherapy Bipolar Trials, the most common adverse reactions leading to discontinuation were anxiety at 1.1% and oral hypoesthesia at 1.1% compared to 0% for placebo. By the way, the threshold being discussed here is a rate equal to or greater than 1% and at least twice the rate of placebo.

When we look at the Adjunctive Bipolar Trial the most common adverse reactions associated with discontinuation rates equal to or greater than 1% and at least twice the rate of placebo in SAPHRIS-treated patients were depression 2.5%; suicidal ideation 2.5%; bipolar disorder 1.9%; insomnia 1.9%; and depressive symptoms 1.3%.

Dr. Birnholz:

Another topic that I want to discuss is dosing. So, Dr. McIntyre, can you speak to us about SAPHRIS dosing?

Dr. McIntyre:

The starting dose for monotherapy with bipolar I disorder in adults is 10 mg BID. This can be reduced to 5 mg BID if warranted by adverse effects. In the monotherapy trials, 90% of the patients remained on 10 mg twice a day. For adjunctive therapy with either

lithium or valproate, the starting dose for SAPHRIS is 5 mg BID. Based on clinical response and tolerability, the dose can be increased to 10 mg twice daily. It's also important to understand that the safety of doses above 10 mg BID has not been evaluated in clinical trials. If SAPHRIS is used for extended periods in bipolar disorder, the healthcare provider should periodically reevaluate the long-term risks and benefits of the drug for the individual patient. The dosing recommendations for SAPHRIS come from the clinical trials. However, the recommended doses will depend on clinical response and tolerability. 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.

Dr. Birnholz:

And, Dr. McIntyre, how is SAPHRIS administered?

Dr. McIntyre:

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, never 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 Bipolar I Disorder 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, have 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 Bipolar I Monotherapy Clinical Trials with SAPHRIS, 5 and 10 mg BID versus placebo, the most commonly observed adverse reactions were somnolence 24% vs 6%, dizziness 11% vs 3%, extrapyramidal symptoms other than akathisia 7% vs 2%, and increased weight 5% vs <1%. And, in the Adult Bipolar I Adjunctive Trial, the most common adverse reactions for SAPHRIS were somnolence 22% vs 10% and oral hypoesthesia 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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