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Office of Surveillance and Epidemiology**

Pediatric Post Marketing Pharmacovigilance Review

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Product Name: Saphris ® (asenapine)

**Pediatric Labeling
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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA), the Office of Surveillance and Epidemiology (OSE) evaluated post-marketing adverse event reports for asenapine in pediatric patients.

Asenapine was first approved by FDA on August 13, 2009 and is currently indicated for the treatment of schizophrenia and bipolar I disorder in adults. Specifically, for bipolar I disorder in adults, it is indicated for the acute treatment of manic or mixed episodes, adjunctive treatment to lithium or valproate, and maintenance monotherapy. The approved pediatric labeling is for acute monotherapy of manic or mixed episodes associated with bipolar I disorder in patients 10 to 17 years of age.

The Division of Pharmacovigilance (DPV) reviewed 129 pediatric reports of adverse events associated with asenapine through August 31, 2017 in the FAERS database. There were no new safety signals identified, no apparent increase in the severity or frequency of any labeled adverse events, and there were no deaths directly associated with asenapine. Due to the lack of serious, unlabeled events, a drug utilization analysis was not included in this review.

Overall, there were no clear patterns of reported adverse events in the FAERS cases to suggest a new safety signal associated with asenapine in pediatric patients. There is no evidence from these data that there are new pediatric safety concerns with this drug at this time. DPV recommends no labeling changes and will continue to monitor adverse events associated with the use of asenapine.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Saphris® (asenapine) is a second-generation atypical antipsychotic and received FDA approval on August 13, 2009. The mechanism of action of asenapine is unknown; however, it has been suggested that the action of asenapine may be mediated through combined antagonist activity at D₂ and 5-HT_{2A} receptors. Asenapine is available in a 2.5 mg, 5 mg and 10 mg sublingual tablet. All dosage strengths are also available in a black cherry flavor. Table 1 below describes the labeled indications and recommended dosing schedule for both the adult and pediatric populations.¹

Table 1. Labeled Indications and Dosing Schedules of Asenapine*			
Patient Population and Indication	Initial Dose†	Recommended Dose	Maximum Dose
Acute and maintenance treatment of schizophrenia in adults	5 mg twice daily	5-10 mg twice daily	10 mg twice daily
Bipolar I Disorder mania in adults: Acute and maintenance monotherapy	5-10 mg twice daily	5-10 mg twice daily	10 mg twice daily
Bipolar I Disorder mania in adults: Adjunct therapy to lithium or valproate	5 mg twice daily	5-10 mg twice daily	10 mg twice daily
Bipolar I Disorder mania monotherapy in pediatric patients age 10 to 17 years‡	2.5 mg twice daily	2.5-10 mg twice daily	10 mg twice daily§

*All routes of administration are sublingual.
†Dose may be titrated upwards every 3 days until at 10 mg twice daily.
‡Pediatric indication emphasized in **bold**.
§Safety of doses greater than 10 mg twice daily is not established.

This Best Pharmaceuticals for Children Act (BPCA) review was triggered as a result of a clinical trial (NCT01244815) in pediatric patients with acute manic or mixed episodes associated with Bipolar I Disorder, conducted by the sponsor as part of a post-marketing requirement (#1496-3) as requested by the Division of Psychiatry Products (DPP) on August 13, 2009. This 3-week, double-blind, placebo-controlled, parallel design trial completed in August 2013 randomized pediatric patients age 10 to 17 years (n = 403) to one of three fixed doses of asenapine (2.5, 5 or 10 mg twice daily) or placebo twice daily. All patients were started at 2.5 mg twice daily and doses were increased every three days until at the dose to which the patient was randomized. In a Phase 1 study, pediatric patients aged 10 to 17 years had an increased incidence of dystonia when the

recommended dose escalation schedule for initial dosing was not followed. Asenapine was demonstrated to be superior to placebo as measured by the change from baseline to Day 21 in the Young Mania Rating Scale (Y-MRS) total score, thereby establishing efficacy. Adverse reactions noted in this trial include somnolence, dizziness, dysgeusia, oral paresthesia, nausea, increased appetite, fatigue (dose-related) and increased weight. No additional new major safety findings were reported from a 50-week, open-label, uncontrolled study. Safety and efficacy for adjunctive therapy in the treatment of Bipolar I Disorder have not been established in the pediatric population.

Efficacy of asenapine was not demonstrated in an 8-week, placebo-controlled, double-blind trial, in 306 adolescent patients aged 12 to 17 years with schizophrenia. Safety and efficacy in patients less than 12 years have not been evaluated when used for schizophrenia. 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 safety trial in pediatric patients with schizophrenia treated with asenapine monotherapy.

This is the first pediatric review completed by OSE for asenapine since its pediatric labeling change on March 12, 2015. There were OSE post-market safety reviews completed for asenapine prior to the pediatric labeling change date that were associated with specific adverse events, specifically hypersensitivity and choking, which are now labeled events. There was also an OSE post market safety review of hearing disorder related events which did not provide sufficient evidence to link asenapine with the described hearing disorders.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis.

-----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 Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack). (5.2)

- *Neuroleptic Malignant Syndrome*: Manage with immediate discontinuation and close monitoring. (5.3)
- *Tardive Dyskinesia*: Discontinue if clinically appropriate. (5.4)
- *Metabolic Changes*: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. (5.5)
- *Orthostatic Hypotension*: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope. (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis*: Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing SAPHRIS if a clinically significant decline in WBC occurs in absence of other causative factors. (5.9)
- *QT Prolongation*: Increases in QT interval; avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval. (5.10)
- *Seizures*: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.12)
- *Potential for Cognitive and Motor Impairment*: Use caution when operating machinery. (5.13)

-----**ADVERSE REACTIONS**-----

The most commonly observed adverse reactions (incidence $\geq 5\%$ and at least twice that for placebo) were (6.1):

- Adult patients with Schizophrenia: akathisia, oral hypoesthesia, and somnolence.
- Bipolar Disorder I Adults (Monotherapy): somnolence, oral hypoesthesia, dizziness, extrapyramidal symptoms (excluding akathisia) and akathisia.
- Bipolar Disorder I Pediatric Patients (Monotherapy): somnolence, dizziness, dysgeusia, oral paresthesia, nausea, increased appetite, fatigue, increased weight.
- Bipolar I Disorder Adults (Adjunctive): somnolence, oral hypoesthesia.

-----**DRUG INTERACTIONS**-----

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

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

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

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System Search Strategy

The Division of Pharmacovigilance (DPV) searched the FDA Adverse Event Reporting System (FAERS) database with the strategy described in Table 2. See Appendix A for a description of the FAERS database.

Table 2. FAERS Search Strategy

Date of Search	September 1, 2017
Time Period of Search	All reports* through August 31, 2017
Search Type	Quick Query
Product Name(s)	Asenapine, asenapine maleate
Search Parameters	All ages, all outcomes, worldwide

*FDA approved Saphris (asenapine) on August 13, 2009

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 3 describes the total number of FAERS reports associated with asenapine for both adults and pediatrics through August 31, 2017.

Table 3. Total Adult and Pediatric FAERS reports* through August 31, 2017 with asenapine

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (<u>≥</u> 18 years)	3110 (2514)	1569 (1102)	167 (129)
Pediatrics (0 - < 18 years)	129 (114)	63 (53)	0 (0)

* May include duplicates and transplacental exposures, and have not been assessed for causality

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

2.2.2 Selection of Pediatric Cases in FAERS

DPV identified 129 pediatric reports of adverse events associated with asenapine use through August 31, 2017 (See Table 3). There were no pediatric deaths reported in FAERS associated with the use of asenapine. All reports were reviewed and were categorized based on the criteria listed below in Table 4.

	Number of Reports (%)
Labeled event	79 (61.2)
Lack of clinical information	17 (13.2)
Indication or Disease-Related	11 (8.5)
No temporal relationship	7 (5.4)
Duplicate report	6 (4.7)
No adverse event described	5 (3.9)
Transplacental or transmammary exposure	4 (3.1)
Total	129 (100%)

2.3 LABELED EVENTS

The most common category utilized during case adjudication was ‘Labeled Events.’ Table 5 describes the five most frequently reported labeled adverse events associated with asenapine, along with the location of the event in the product labeling. These events comprised 59% of all labeled events that were reported. Each of the remaining labeled events occurred fewer than four times in the reviewed reports.

	Number of Reports (%)	Product Labeling Location
Hypersensitivity Reactions*†	16 (20)	5.6 W/P
Extrapyramidal Symptoms (EPS)‡	13 (16.5)	6.1 Clinical Trials Experience
Hypoesthesia Oral	7 (8.9)	6 Adverse Reactions
Suicidal Ideation	6 (7.6)	6.1 Clinical Trials Experience
Nausea/Vomiting	5 (6.3)	6.1 Clinical Trials Experience
Total	47 (59%)	

*Hypersensitivity reactions reported included anaphylaxis, urticaria, rash and tongue swelling

†Enhanced pharmacovigilance (EPV) plan in place that requires the sponsor to submit all reports related to hypersensitivity to FDA as an expedited (15-day) report²

‡Extrapyramidal symptoms reported included dystonia, oculogyric crisis, dyskinesia, tardive dyskinesia and parkinsonism.

2.4 LACK OF CLINICAL INFORMATION

The second most common category utilized during case adjudication was ‘Lack of Clinical Information.’ Reports were placed in this category if they were missing essential information for assessing causality, such as treatment dates for asenapine, time to onset of adverse event, action taken with asenapine, or outcome of events. These reports comprised approximately 22% of the total reports retrieved using the FAERS search strategy in Section 2.1. While comprehensive review of these reports was performed, in all cases the lack of one or more of the above factors precluded assessment of causality.

2.5 INDICATION OR DISEASE-RELATED EVENTS

The third most common category utilized during case adjudication was ‘Indication or Disease-Related.’ The cases placed in this category described adverse events related to exacerbation of underlying disease, most often bipolar I disorder and schizophrenia. Some of the events reported included “bipolar crisis,” worsening of hallucinations, worsening of mania, agitation, and reemergence of previous bipolar symptoms. These events were all determined to be manifestations of the disease for which the patient was undergoing treatment with asenapine.

Generally, for all therapeutic products, the category of adverse events consistent with lack of efficacy or decreased efficacy are the most common types of adverse events reported in post marketing cases. The preferred term *lack of effect* alone accounts for approximately 6% to 7% of all adverse event terms reported in FAERS cases. For many psychiatric conditions including bipolar disorder, depression, schizophrenia, and other mood and psychotic disorders, these disorders are typically episodic, chronic, and often do not respond fully to even ideal courses of medication and other treatment. Thus, we expect that many patients with these conditions will experience relapse of symptoms, despite treatment, as part of the natural history of the disorders; and we expect to receive reports of suspected lack of effect and related adverse events for virtually any therapeutic product.

Reviewer’s Comment: The vast majority of such reported adverse events are not attributable to the therapeutic product of interest. In our experience in investigating reported lack of effect reported with various products, most such analyses indicate that there is no evidence of product quality problems, lack of bioequivalence between relevant products, or therapeutic inequivalence between particular products of interest. However, there are rare cases in which there is a clearly identified product quality problem, lack of bioequivalence, therapeutic inequivalence between innovator and generic products, or other unique situations. There are certain types of products that theoretically might pose greater risk of problems with therapeutic inequivalence or bioinequivalence; typically these include products with a narrow therapeutic index, modified-release products, and products with other complex features.

3 DISCUSSION

DPV reviewed 129 pediatric reports of adverse events associated with asenapine use through August 31, 2017 in the FAERS database. There were no unlabeled events, no new safety signals identified, no apparent increased severity or frequency of labeled adverse events, and there were no deaths directly associated with asenapine use in pediatric patients. Reports were categorized based on the following criteria: described a labeled event, lacked clinical information, determined to be indication- or disease-related, included no description of an adverse event, lacked temporal association with asenapine, was a duplicate report, or was a result of transplacental or transmammary exposure.

The most frequently reported labeled adverse events were hypersensitivity reactions, EPS, oral hypoesthesia, suicidal ideation and nausea/vomiting. These reports comprised 59% of all labeled events that were reported. Each of the remaining labeled events occurred fewer than four times in the reviewed reports. Hypersensitivity reactions is currently associated with an enhanced pharmacovigilance (EPV) plan for asenapine requiring 15-day expedited reporting of both serious and non-serious outcomes for all hypersensitivity reactions including anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue, dyspnea, wheezing, rash, and other clinically significant reactions related to hypersensitivity.² The reports reviewed here were in line with current labeling for hypersensitivity reactions in section 5.6 WARNINGS AND PRECAUTIONS.

Approximately 22% of the FAERS reports associated with pediatric use of asenapine were missing key clinical information necessary to link asenapine with the reported adverse event. The remaining 19% of reports were either indication- or disease-related, did not describe an adverse event, lacked a temporal association with asenapine, was a duplicate report, or described transplacental or transmammary exposure.

Due to the lack of serious, unlabeled events, a drug utilization analysis was not included in this review.

4 CONCLUSION

There were no clear patterns of reported adverse events in the FAERS cases to suggest a new safety signal associated with asenapine in pediatric patients. There is no evidence from these data that there are any new pediatric safety concerns with asenapine at this time.

5 RECOMMENDATIONS

DPV recommends no regulatory action at this time, and will continue to monitor adverse events associated with the use of asenapine.

6 REFERENCES

1 Saphris [Package Insert]. Irvine, CA: Allergan USA.; February 2017 (Accessed August 31, 2017).

2 Sagoo, SK. Supplement Approval Letter: NDA 22117/S-010 Saphris (asenapine). United States Food and Drug Administration Reference ID 2997519. DARRTS 2011 August 9.

7 APPENDICES

7.1 APPENDIX A FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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