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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance

Date:	March 2, 2021
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Product Name:	Aptiom (eslicarbazepine acetate)
Pediatric Labeling Approval Date:	September 13, 2017
Application Type/Number:	NDA 022416
Applicant:	Sunovion Pharmaceutical Inc.
OSE RCM #:	2021-222

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports in pediatric patients less than 18 years of age reported with Aptiom (eslicarbazepine acetate) use. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA), the Pediatric Research Equity Act (PREA), and Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with eslicarbazepine in the pediatric population.

The FDA approved eslicarbazepine for the treatment of partial-onset seizures (POS) in pediatric patients 4 years and older on September 13, 2017. The safety and effectiveness of eslicarbazepine in pediatric patients below 4 years of age have not been established.

Our FAERS search did not identify any fatal or serious unlabeled pediatric adverse event reports associated with eslicarbazepine from September 13, 2016 to November 17, 2020.

DPV-I did not identify any pediatric safety concerns for eslicarbazepine at this time. DPV-I recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of eslicarbazepine.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Aptiom (eslicarbazepine) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA), Pediatric Research Equity Act (PREA), and Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with eslicarbazepine use in pediatric patients.

1.1 REGULATORY HISTORY

Eslicarbazepine acetate (Aptiom) is a once daily orally administered antiepileptic drug (AED).[1] It is currently indicated for the treatment of partial-onset seizures (POS) in patients 4 years of age and older.[1] Eslicarbazepine was approved in pediatric patients 4 years and older on September 13, 2017.[2] The safety and effectiveness of eslicarbazepine in pediatric patients below 4 years of age have not been established. Eslicarbazepine was first approved by FDA for the treatment of partial onset seizures in patients 18 years and older as adjunctive therapy in 2013 and monotherapy in 2015. The precise mechanism by which eslicarbazepine exerts anticonvulsant activity is unknown but is thought to involve inhibition of voltage-gated sodium channels.[1] It is chemically related to the AEDs carbamazepine and oxcarbazepine. It is considered a third-generation AED member of the dibenzazepine anticonvulsant family in which carbamazepine would be considered first generation and oxcarbazepine as second generation.[2] This review was triggered by pediatric studies completed under PREA and BPCA after the approval of eslicarbazepine in pediatric patients 4 years of age and older on September 13, 2017.

The safety and tolerability of eslicarbazepine for the treatment of partial onset seizures in pediatric patients aged 4-17 years was supported by three studies. One was an open-label Phase 2 study of pharmacokinetics and safety of eslicarbazepine in patients with refractory POS aged 4-17 years. The other two were randomized, placebo-controlled trials of eslicarbazepine as adjunct therapy in patients with refractory POS who were 4-17 years of age. Additionally, safety results from adolescent patients enrolled in adult studies of eslicarbazepine were also analyzed but not pooled with the three primary studies.[2] Across the studies in pediatric patients with POS, 393 pediatric patients ages 4-17 years received eslicarbazepine, of whom 265 received eslicarbazepine for at least one year. Adverse reactions reported in clinical studies of pediatric patients 4-17 years of age were similar to those seen in adult patients. The pharmacokinetic analysis provided support for doses in the pediatric population that provide similar exposures to efficacious doses in the adult population.[1]

The Office of Surveillance and Epidemiology (OSE) and the Office of New Drugs (OND) previously evaluated postmarketing adverse event reports for eslicarbazepine use in all age groups that was summarized in a FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary Analysis ("915-safety review"), completed on May 30, 2017.[2,3] The 915-safety review is a routine postmarketing safety evaluation performed 18 months after approval of eslicarbazepine and/or after use of eslicarbazepine by at least 10,000 patients. This review identified Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) and hematologic events independent of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) as new safety signals that were added to the WARNINGS and PRECAUTIONS section of the

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eslicarbazepine labeling. Two additional safety signals were also identified during the 915 review, namely pancreatitis and atrioventricular (AV) block. However, none of the cases suggested a probable causality and the causal relationship to eslicarbazepine was unclear. Therefore, the 915-safety team opted to continue postmarket monitoring.[2,3] OSE has not previously completed a pediatric postmarketing pharmacovigilance review for eslicarbazepine.

1.2 RELEVANT LABELED SAFETY INFORMATION

The eslicarbazepine labeling contains the following safety information within the Highlights of Prescribing Information.[1]

CONTRAINDICATIONS

Hypersensitivity to eslicarbazepine acetate or oxcarbazepine. (4)

WARNINGS AND PRECAUTIONS

- Suicidal Behavior and Ideation: Monitor for suicidal thoughts or behavior. (5.1)
- Serious Dermatologic Reactions, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Anaphylactic Reactions and Angioedema: Monitor and discontinue if another cause cannot be established. (5.2, 5.3, 5.4)
- Hyponatremia: Monitor sodium levels in patients at risk or patients experiencing hyponatremia symptoms. (5.5)
- Neurological Adverse Reactions: Monitor for dizziness, disturbance in gait and coordination, somnolence, fatigue, cognitive dysfunction, and visual changes. Use caution when driving or operating machinery. (5.6)
- Withdrawal of APTIOM: Withdraw APTIOM gradually to minimize the risk of increased seizure frequency and status epilepticus. (2.6, 5.7, 8.1)
- Drug Induced Liver Injury: Discontinue APTIOM in patients with jaundice or evidence of significant liver injury. (5.8)
- Hematologic Adverse Reactions: Consider discontinuing. (5.10)

ADVERSE REACTIONS

- Most common adverse reactions in adult patients receiving APTIOM (≥4% and ≥2% greater than placebo): dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor. (6.1)
- Adverse reactions in pediatric patients are similar to those seen in adult patients.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*

Date of search	November 18, 2020
Time period of search	September 13, 2016† - November 17, 2020
Search type	FBIS Quick Query
Product terms	Product active ingredient: eslicarbazepine, eslicarbazepine acetate
MedDRA Search Terms (Version 23.1)	All Preferred Terms (PTs)

* See Appendix A for a description of the FAERS database.
† One year prior to U.S. pediatric labeling approval date of eslicarbazepine
Abbreviations: FBIS=FDA Business Intelligence System, MedDRA=Medical Dictionary for Regulatory Activities

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3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from September 13, 2016 (one year prior to pediatric labeling approval date of eslicarbazepine) to November 17, 2020.

Table 2. Total Adult and Pediatric Eslicarbazepine FAERS Reports* Received by FDA From September 13, 2016 to November 17, 2020

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	505 (328)	388 (211)	29 (19)
Pediatrics (0 - <18 years)	59 (42)	44 (27)	0 (0)

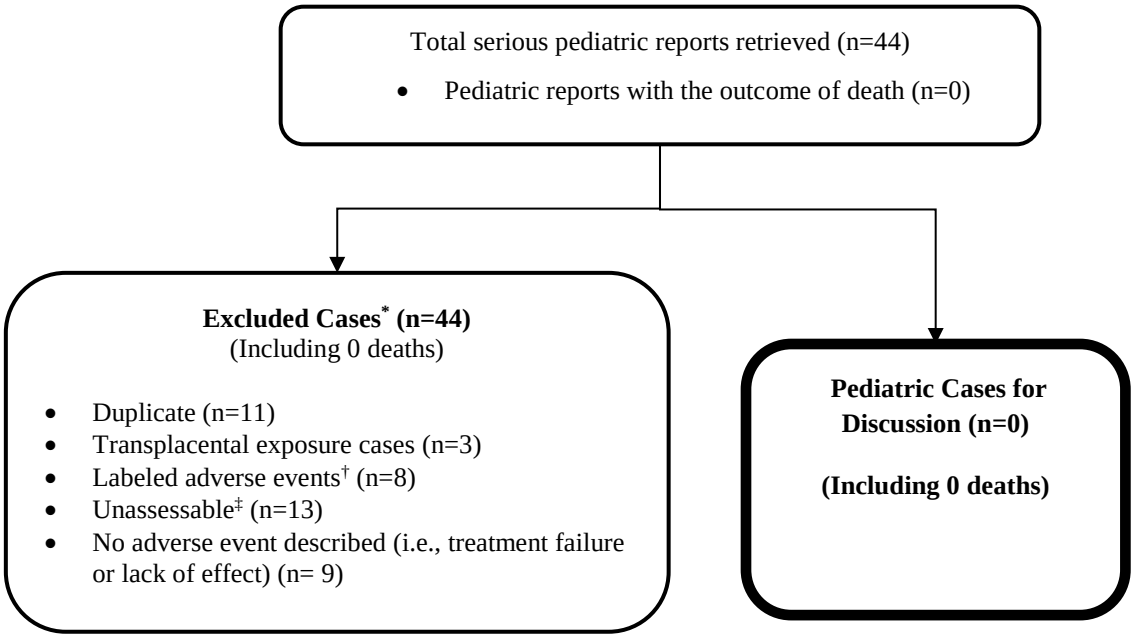
* May include duplicates and transplacental exposures, and have not been assessed for causality

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

3.1.2 Selection of Pediatric Cases in FAERS

Our FAERS search retrieved 44 serious pediatric reports from September 13, 2016 to November 17, 2020. DPV-I reviewed all 44 pediatric reports and excluded reports from further analysis if they described labeled adverse events that did not reflect an apparent increase in severity of the labeled events. We further excluded reports from the case series for various reasons, such as duplicate reports, transplacental exposure, the adverse event was unlikely to be causally related to the use of eslicarbazepine (e.g., co-morbid diseases or concomitant medications provide a more likely explanation for the adverse events), no adverse event described (i.e., treatment failure or lack of effect), and unassessable cases (i.e., cases that cannot be clinically assessed for causality because information is insufficient or lacking). **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Pediatric Cases Associated with Eslicarbazepine Use



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above
† Includes the following eslicarbazepine labeled adverse events: DRESS, hyponatremia, angioedema, peripheral edema, visual disturbances and Stevens-Johnson Syndrome.
‡ Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, or clinical course and outcome).

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event reports associated with eslicarbazepine.

3.1.4 Summary of Non-Fatal Serious Pediatric Cases (N=0)

We did not identify any serious unlabeled non-fatal adverse event reports associated with eslicarbazepine in the pediatric population.

4 DISCUSSION

DPV-I reviewed all the serious FAERS reports associated with eslicarbazepine use in the pediatric population (ages 0 to < 18 years) from September 13, 2016 through November 17, 2020. Since that time, the majority of the FAERS reports described serious adverse events that were consistent with known and labeled adverse events described in the eslicarbazepine approved prescribing information.[1] We did not identify an increase in severity in the labeled serious adverse events associated with eslicarbazepine. There were no pediatric deaths reported with eslicarbazepine use during the examined time period. Of the total pediatric serious FAERS reports evaluated, we did not identify any serious unlabeled non-fatal adverse events associated with eslicarbazepine use in the pediatric population. Additionally, no reports were identified for the two safety signals identified during the 915-safety review completed in 2017 that are not included in the eslicarbazepine prescribing information at this time (i.e., pancreatitis, AV block).

5 CONCLUSION

DPV-I did not identify any pediatric safety concerns associated with eslicarbazepine use at this time.

6 RECOMMENDATION

DPV-I recommends no regulatory action specific to pediatric patients at this time, and will continue to monitor all adverse events associated with the use of eslicarbazepine in the pediatric population.

7 REFERENCES

1. Aptiom (eslicarbazepine acetate) [Package insert] Sunovion Pharmaceuticals Inc. Marlborough, MA. 2019
2. Getzoff, Natalie. Aptiom (eslicarbazepine acetate) Clinical (Medical) Review NDA 022416 (S-009). https://www.fda.gov/media/109097/download.
3. Long, Karen. Aptiom (eslicarbazepine) FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary Analysis. NDA 022416 . May 30, 2017. https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8043fd4c.

8 APPENDICES

8.1 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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council 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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