Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	May 1, 2023
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Product Name:	Vimpat (lacosamide)
Pediatric Labeling Approval Dates:	November 3, 2017 November 16, 2020 October 14, 2021
Application Type/Number:	NDA 022253 NDA 022254 NDA 022255
Applicant:	UCB, Inc.
TTT Record ID:	2022-2801

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Vimpat (lacosamide) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with lacosamide in pediatric patients.

The FDA initially approved lacosamide as an oral tablet and as an intravenous solution on October 28, 2008. Lacosamide oral solution was approved on April 20, 2010. Lacosamide is currently indicated for the treatment of partial-onset seizures in patients 1 month of age and older and as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients 4 years of age and older. This pediatric postmarketing safety review for lacosamide was stimulated by the pediatric labeling changes on November 3, 2017, November 16, 2020, and October 14, 2021 that expanded the use of lacosamide in the pediatric population.

DPV reviewed all U.S. serious FAERS reports with lacosamide in the pediatric population (0 - <17 years of age) from November 3, 2016 through November 14, 2022 and did not identify any cases for inclusion in a case series.

DPV did not identify any new pediatric safety concerns for lacosamide at this time and will continue to monitor all adverse events associated with the use of lacosamide.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Vimpat (lacosamide) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with lacosamide in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Vimpat (lacosamide) is a functionalized amino acid, initially approved for marketing in the U.S. on October 28, 2008, as an oral tablet (NDA 022253) and as an intravenous solution (NDA 022254). Lacosamide oral solution (NDA 022255) was approved on April 20, 2010. Lacosamide is currently indicated for the treatment of partial-onset seizures in patients 1 month of age and older and as adjunctive therapy in the treatment of primary generalized tonic-clonic (PGTC) seizures in patients 4 years of age and older.[1]

This pediatric postmarketing safety review for lacosamide was stimulated by the pediatric labeling changes represented in Table 1.

Table 1. Pediatric Labeling Changes and Clinical Trial Summary for Lacosamide

Date/ Application Number	Labeling Change Summary[2]	Clinical Trial Summary
November 3, 2017/ NDA 022253 NDA 022255	VIMPAT is indicated for the treatment of partial-onset seizures in patients 4 years of age and older. Safety and effectiveness of VIMPAT tablets and oral solution have been established in pediatric patients 4 to less than 17 years of age. Safety of VIMPAT injection in pediatric patients has not been established. Safety and effectiveness in pediatric patients below the age of 4 years have not been established.[3]	The use of lacosamide in pediatric patients 4 to < 17 years of age is supported by evidence from adequate and well-controlled studies of lacosamide in adults with partial-onset seizures, pharmacokinetic data from adult and pediatric patients, and safety data in 328 pediatric patients 4 to <17 years of age. The pediatric pharmacokinetic profile of lacosamide was determined in a population pharmacokinetic analysis in two open-label studies in 79 pediatric patients with partial-onset seizures in patients 4 years to <17 years of age. Both apparent clearance and apparent volume of distribution increase as body weight increases. Steady state plasma concentrations are achieved after 3 days of twice daily repeated administration. The pharmacokinetics of lacosamide in pediatric patients are similar when used as monotherapy or as adjunctive therapy for the treatment of partial-onset seizures.[4]

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Table 1. Pediatric Labeling Changes and Clinical Trial Summary for Lacosamide		
Date/ Application Number	**Labeling Change Summary[2]**	**Clinical Trial Summary**
November 16, 2020/ NDA 022253	Safety and effectiveness of VIMPAT as adjunctive therapy in the treatment of PGTC seizures in pediatric patients with idiopathic generalized epilepsy 4 years and older was established in a 24-week double-blind, randomized, placebo-controlled, parallel-group, multi-center study (Study 5), which included 37 pediatric patients 4 years to < 17 years. VIMPAT injection is indicated for the treatment of partial-onset seizures (POS) in pediatric patients 4 years and older. Safety and effectiveness in pediatric patients below the age of 4 years have not been established.[5]	The study consisted of patients, 4 years to < 17 years on a stable dose of 1 to 3 antiepileptic drugs experiencing at least 3 documented PGTC seizures during a baseline period. A fixed-dose regimen initiated at a dose of 2 mg/kg/day in patients weighing < 50 kg or 100 mg/day in patients weighing 50 kg or more to achieve a maintenance dose of 12 mg/kg/day in patients weighing <30 kg, 8 mg/kg/day in patients weighing 30 to <50 kg, or 400 mg/day in patients weighing 50 kg or more. Lacosamide injection can be administered intravenously with the same dosing regimens described for oral dosing. The primary efficacy endpoint was time to second PGTC seizure and the key secondary efficacy endpoint was the percentage of patients not experiencing a PGTC during the 24-week treatment period. The risk of developing a second PGTC seizure was statistically significantly lower in lacosamide group than in the placebo group during the 24-week treatment period.[6]
October 14, 2021/ NDA 022253 NDA 022254 NDA 022255	Safety and effectiveness for the treatment of partial-onset seizures have been established in pediatric patients 1 month to less than 4 years; previously approved down to 4 years and older.[7]	847 patients 1 month to <17 years of age received lacosamide oral solution or tablet and adverse reactions reported in the clinical studies were similar to those seen in adult patients. 103 patients 1 month to <17 years of age with epilepsy received lacosamide infusions administered over a 30 to 60 minute time period. The adverse reactions associated with lacosamide injection in pediatric patients is expected to be similar to those noted in adults.[8]
Abbreviations: NDA=new drug application, PGTC= primary generalized tonic-clonic, POS= partial-onset seizures		

DPV has not previously presented an evaluation of postmarketing adverse event reports for lacosamide in pediatric patients to the Pediatric Advisory Committee (PAC).

1.2 RELEVANT LABELED SAFETY INFORMATION

The Boxed Warning, Contraindications, Warnings and Precautions, Adverse Reactions (from the Highlights of Prescribing Information), and the Pediatric Use sections of the lacosamide product labeling are reproduced below.

----------CONTRAINDICATIONS----------

- None

----------WARNINGS AND PRECAUTIONS----------

- Monitor patients for suicidal behavior and ideation
- VIMPAT may cause dizziness and ataxia
- Cardiac Rhythm and Conduction Abnormalities: Obtaining ECG before beginning and after titration to steady-state maintenance is recommended in patients with underlying proarrhythmic conditions or on concomitant
- Beginning and after titration to steady-state maintenance is recommended in patients with underlying proarrhythmic conditions or on concomitant medications that affect cardiac conduction; closely monitor these patients
- VIMPAT may cause syncope
- VIMPAT should be gradually withdrawn to minimize the potential of increased seizure frequency
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Multi-Organ Hypersensitivity: Discontinue if no alternate etiology

----------ADVERSE REACTIONS----------

- Adjunctive therapy: Most common adverse reactions in adults (≥10% and greater than placebo) are diplopia, headache, dizziness, nausea, and somnolence
- Monotherapy: Most common adverse reactions are similar to those seen in adjunctive therapy studies
- Pediatric patients: Adverse reactions are similar to those seen in adult patients

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

8.4 Pediatric Use

Partial-Onset Seizures

Safety and effectiveness of VIMPAT for the treatment of partial-onset seizures have been established in pediatric patients 1 month to less than 17 years of age. Use of VIMPAT in this age group is supported by evidence from adequate and well-controlled studies of VIMPAT in adults with partial-onset seizures, pharmacokinetic data from adult and pediatric patients, and safety data in 847 pediatric patients 1 month to less than 17 years of age.

Safety and effectiveness in pediatric patients below 1 month of age have not been established.

Primary Generalized Tonic-Clonic Seizures

Safety and effectiveness of VIMPAT as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in pediatric patients with idiopathic generalized epilepsy 4 years of age and older was established in a 24-week double-blind, randomized, placebo-controlled, parallel-group, multi-center study (Study 5), which included 37 pediatric patients 4 years to less than 17 years of age.

Safety and effectiveness in pediatric patients below the age of 4 years have not been established.

Animal Data

Lacosamide has been shown in vitro to interfere with the activity of collapsin response mediator protein-2 (CRMP-2), a protein involved in neuronal differentiation and control of axonal outgrowth. Potential related adverse effects on CNS development cannot be ruled out. Administration of lacosamide to rats during the neonatal and juvenile periods of postnatal development (approximately equivalent to neonatal through adolescent development in humans) resulted in decreased brain weights and long-term neurobehavioral changes (altered open field performance, deficits in learning and memory). The no-effect dose for developmental neurotoxicity in rats was associated with a plasma lacosamide exposure (AUC) less than that in humans at the maximum recommended human dose of 400 mg/day.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of search	November 15, 2022
Time period of search	November 3, 2016† - November 14, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Lacosamide
MedDRA search terms (Version 25.1)	All PT terms
* See Appendix A for a description of the FAERS database. † One year prior to the first pediatric labeling change. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from November 3, 2016, through November 14, 2022 with lacosamide.

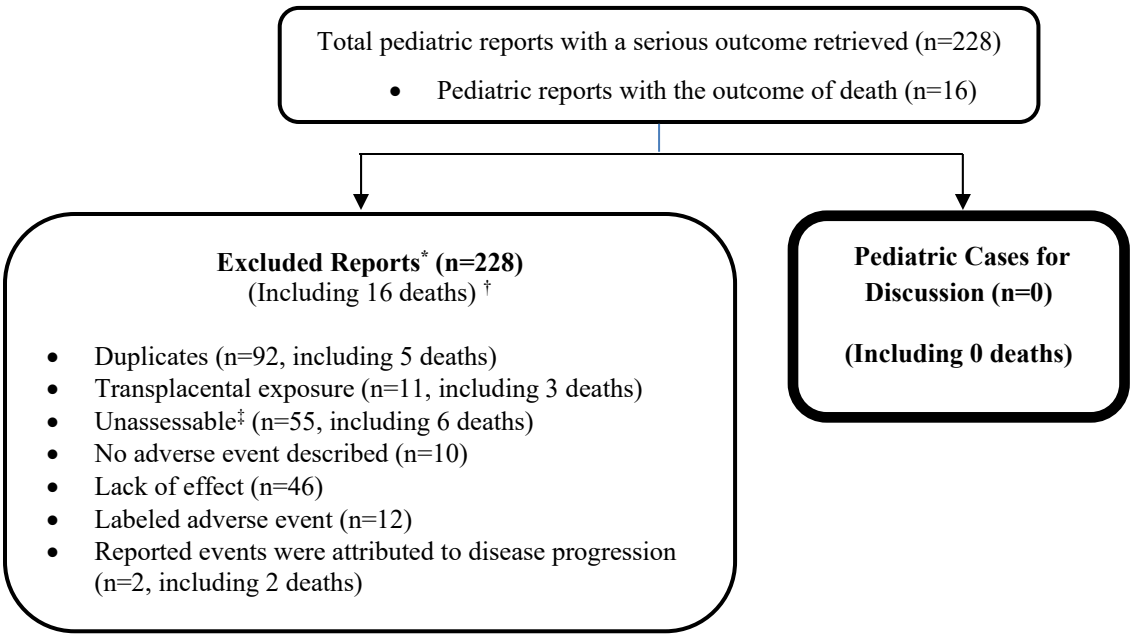
Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From November 3, 2016, through November 14, 2022 with Lacosamide			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	6,560 (3,032)	5,901 (2,465)	839 (444)
Pediatrics (0 - <17 years)	1,070 (375)	897‡ **(228)**	39‡ **(16)**
* 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. ‡ Eleven additional reports of pediatric deaths were identified among reports not reporting an age (n=6) and death not coded in the Outcomes field (n=5). These reports are reflected in the count of pediatric reports.			

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 228 U.S. serious pediatric reports from November 3, 2016, through November 14, 2022.

No cases were identified for inclusion in a pediatric case series. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded reports from the case series for the following reasons: the adverse event was already adequately listed in the product labeling; the reported adverse events were more likely due to disease progression; no adverse event was described in the report; report of lack of effect (without associated adverse event); duplicate reports; reports of transplacental exposure; or the report was unassessable because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), or the information is contradictory or information provided in the case cannot be supplemented or verified.

Figure 1. Selection of Serious U.S. Pediatric Cases with lacosamide



* DPV reviewed these reports, but they were excluded from further discussion for the reasons listed above

† Sixteen excluded U.S. FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to lacosamide. These reports were excluded for the following reasons: the report did not provide sufficient clinical detail to assess causality (n=6); the report is a duplicate (n=5); the deaths occurred following transplacental exposure to lacosamide (n=3). The two remaining fatal reports describe pediatric patients with complex medical histories. 1) A 13-year-old male with treatment failure on multiple antiepileptic drugs for super-refractory myoclonic status epilepticus that led to progressive neurological dysfunction and death; 2) A 12-year-old female with fumarate hydratase deficiency (FHD) who received lacosamide off-label for epileptic spasms and tonic seizures. Treatment with lacosamide was reported as effective and no adverse event was reported. The patient died at the age of 16 due to the progression of FHD.

‡ Unassessable: Report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any FAERS U.S. fatal pediatric adverse event cases associated with lacosamide in the pediatric population for discussion.

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

We did not identify any FAERS U.S. serious, unlabeled, non-fatal adverse event cases associated with lacosamide in the pediatric population.

4 DISCUSSION

DPV reviewed 228 FAERS U.S. serious reports with lacosamide in the pediatric population (ages 0 - <17 years) from November 3, 2016, through November 14, 2022. We identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with lacosamide.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for lacosamide at this time.

6 RECOMMENDATION

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

7 REFERENCES

1. Vimpat (lacosamide) [package insert]. Smyrna, GA. UCB, Inc. Revised September 2022.

2. Pediatric Labeling Changes Spreadsheet. Available at: https://www.fda.gov/media/165037/download. Accessed: March 3, 2023

3. Vimpat (lacosamide) [package insert]. Smyrna, GA. UCB, Inc. Revised November 2017.

4. Freilich ER. Clinical Review. September 29, 2017. Division of Neurology Products. Available at: https://www.fda.gov/media/112248/download Accessed: March 3, 2023.

5. Vimpat (lacosamide) [package insert]. Smyrna, GA. UCB, Inc. Revised November 2020.

6. Freilich ER. Clinical Review. October 16, 2020. Division of Neurology Products. Available at: https://www.fda.gov/media/144647/download Accessed: March 3, 2023.

7. Vimpat (lacosamide) [package insert]. Smyrna, GA. UCB, Inc. Revised October 2021.

8. Freilich ER. Clinical Review September 29, 2021. Division of Neurology Products. Available at: https://www.fda.gov/media/155312/download Accessed March 3, 2023.

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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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