**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**
**Office of Pharmacovigilance and Epidemiology**

# Pediatric Postmarketing Pharmacovigilance Review

| | |
|---|---|
| **Date:** | October 4, 2022 |
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| **Product Name:** | Fycompa (perampanel) |
| **Pediatric Labeling Approval Date:** | September 27, 2018 |
| **Application Type/Number:** | NDA 202834 (tablet), NDA 208277 (suspension) |
| **Applicant:** | Eisai, Inc |
| **TTT #:** | 2022-1251 |

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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Fycompa (perampanel) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV)-I conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with perampanel in pediatric patients.

The FDA approved perampanel on October 22, 2012, for the adjunctive therapy in the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. Since that time, perampanel has received approval for a new indication of adjunctive therapy for the treatment of primary generalized tonic-clonic (PGTC) seizures in patients with epilepsy 12 years of age and older. The approved pediatric labeling is for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 4 years of age and older, and for the adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older. This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling changes on September 27, 2018.

We reviewed all FAERS U.S. serious cases with perampanel in the pediatric population (ages 0 to <17 years) during the period of February 1, 2019, through September 7, 2022. Our evaluation identified one case describing hair curling and one case describing developmental regression associated with perampanel use; however, there is insufficient evidence to support a new signal at this time. We did not identify any additional safety signals, increased severity or frequency of any labeled adverse events, or deaths directly associated with perampanel.

DPV-I did not identify any new pediatric safety concerns for perampanel 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 perampanel.

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for perampanel in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV)-I conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with perampanel in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

Fycompa (perampanel), a non-competitive AMPA glutamate receptor antagonist, was initially approved as oral tablets by the FDA on October 22, 2012, for the adjunctive therapy in the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.[1] On June 19, 2015, the FDA approved a new indication of adjunctive therapy for the treatment of primary generalized tonic-clonic (PGTC) seizures in patients with epilepsy 12 years of age and older.[2]

On April 29, 2016, the FDA approved perampanel oral suspension for the adjunctive therapy in the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 12 years of age and older and as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older.[3]

On July 26, 2017, the FDA approved the expanded use of perampanel oral tablets and suspension as monotherapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.[4]

On September 27, 2018, the FDA approved the expansion of the use of perampanel tablets and oral suspension for the treatment of partial onset seizures, with or without secondarily generalized seizures, to include patients 4 years of age and older based on extrapolation of efficacy data in the population aged 12 years and above, and pharmacokinetic analyses that support the conclusion that the same dosing recommendations can be applied to all age groups from age 4 years through adulthood.[5]

Fycompa (perampanel) is currently indicated for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 4 years of age and older; and for the adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older.[6] Fycompa is supplied as 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg oral tablets, and 0.5 mg/ml oral suspension.

The Office of Surveillance and Epidemiology (OSE) previously evaluated pediatric postmarketing adverse event reports and drug utilization data with perampanel in a review dated August 3, 2015,[7] which was prompted by the initial approval for perampanel on October 22, 2012. DPV-I also performed an evaluation dated May 3, 2019,[8] that was prompted by three labeling changes, dated June 19, 2015, April 29, 2016, and July 26, 2017. OSE's evaluations did not identify any new pediatric safety concerns, and recommended routine monitoring for adverse events with perampanel.



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This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling changes on September 27, 2018.

### 1.2 RELEVANT LABELED SAFETY INFORMATION

A summary of the safety information from the HIGHLIGHTS OF PRESCRIBING INFORMATION section and Pediatric Use subsection of the perampanel product labeling is reproduced below.[6]

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

None

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

- Suicidal Behavior and Ideation: Monitor for suicidal thoughts or behavior (5.2)
- Neurologic Effects: Monitor for dizziness, gait disturbance, somnolence, and fatigue (5.3)
- Patients should use caution when driving or operating machinery (5.3)
- Falls: Monitor for falls and injuries (5.4)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Multi-Organ Hypersensitivity: Discontinue if no alternate etiology (5.5)
- Withdrawal of Antiepileptic Drugs: In patients with epilepsy, there may be an increase in seizure frequency (5.6)

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

Most common adverse reactions (≥5% and ≥1% higher than placebo) include dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, headache, vomiting, contusion, abdominal pain, and anxiety (6.1)

*Partial-Onset Seizures*

Adverse reactions in pediatric patients 4 to <12 years of age were similar to those seen in patients 12 years of age and older.

8 USE IN SPECIFIC POPULATIONS

8.4 *Pediatric Use*

Safety and effectiveness of FYCOMPA for the treatment of partial-onset seizures have been established in pediatric patients 4 years of age and older.

The safety and effectiveness of FYCOMPA in patients 12 years of age and older was established by three randomized double-blind, placebo-controlled, multicenter studies, which included 72 pediatric patients between 12 and 16 years of age exposed to FYCOMPA [see Clinical Pharmacology (12.3) and Clinical Studies (14.1)]. Use of FYCOMPA for the treatment of partial-onset seizures in pediatric patients 4 years to less than 12 years of age is supported by evidence from adequate and well-controlled studies of FYCOMPA in patients 12 years of age and older with partial onset seizures, pharmacokinetic data from adult and pediatric patients, and safety data in 225 pediatric patients 4 years to less than 12 years of age treated with FYCOMPA [see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)].

The safety and efficacy of FYCOMPA for the adjunctive therapy of primary generalized tonic-clonic seizures in pediatric patients 12 years of age and older was established in a single randomized double-blind, placebo-controlled, multicenter trial (n=164), which included 11 pediatric patients 12 to 16 years of age exposed to FYCOMPA; an additional 6 patients were treated with FYCOMPA in the open-label extension of the study [see Clinical Studies (14.2)].

The safety and effectiveness of FYCOMPA for the treatment of partial-onset seizures in pediatric patients less than 4 years of age or for the treatment of primary generalized tonic-clonic seizures in pediatric patients less than 12 years of age have not been established.

# 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 | September 8, 2022 |
| Time period of search | February 1, 2019† - September 7, 2022 |
| Search type | RxLogix PV Reports Quick Query |
| Product terms | Product active ingredient: Perampanel |
| MedDRA search terms (Version 25.0) | All PT terms |

* See Appendix A for a description of the FAERS database.
† Data end date of previous DPV-I Pediatric Postmarketing Pharmacovigilance Review for perampanel was January 31, 2019[8]
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 2 presents the number of adult and pediatric FAERS reports from February 1, 2019, through September 7, 2022, with perampanel.

| **Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From February 1, 2019 through September 7, 2022 With Perampanel** | | | |
|---|---|---|---|
| | **All reports (U.S.)** | **Serious† (U.S.)** | **Death (U.S.)** |
| Adults (≥ 17 years) | 817 (126) | 753 (79) | 28 (2) |
| Pediatrics (0 - <17 years) | 287 (37) | **271 (25)** | **14 (1)** |

* 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 U.S. Serious Pediatric Cases in FAERS*

Our FAERS search retrieved 25 U.S. serious pediatric reports from February 1, 2019, through September 7, 2022.

We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded reports from the case series for various reasons, such as duplicate reports, adverse event more likely due to comorbidities, unassessable reports, no adverse event described, labeled adverse event without new features.

Figure 1 presents the selection of cases for the pediatric case series.



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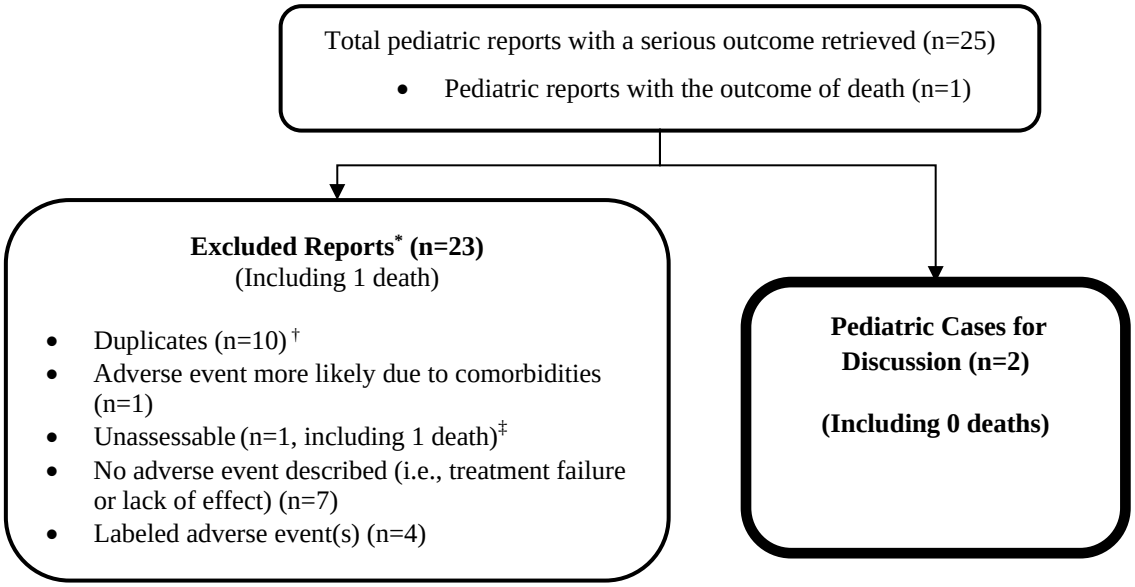
**Figure 1. Selection of Serious U.S. Pediatric Cases with Perampanel**




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

† This includes one case that reported pancreatitis with cholelithiasis, which was identified in previous DPV-I pediatric postmarket pharmacovigilance review[8]

‡ 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), the information is contradictory, or information provided in the report cannot be supplemented or verified. This included one death report in the setting of multi-drug resistant refractory status epilepticus that was complicated by refractory hypotension, renal failure, and respiratory failure; however, the case provided insufficient information for causality assessment.

#### *3.1.3 Summary of Fatal Pediatric Cases (N=0)*

There are no fatal pediatric adverse event cases for further discussion.

#### *3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=2)*

We identified two serious FAERS cases with perampanel in the U.S. pediatric population reporting a non-fatal serious outcome. Appendix B contains a line listing of the cases. The two cases are summarized below:

**FAERS Case#17988482; MCN: US-LUPIN PHARMACEUTICALS INC.-2019-07866:**[9]

- A literature case reported a 13-year-old female patient was treated with perampanel 2 mg daily for refractory epilepsy after lamotrigine treatment failure. Medical history included developmental delay and stereotypy due to genetically confirmed Pitt-Hopkins syndrome. Concomitant medications included valproate and levetiracetam for 16 months, and medroxyprogesterone. Approximately a few weeks after the introduction of perampanel, the patient's mother noticed hair curling in the occipital area that extended to the whole head in the following weeks. No change in hair texture was noticed. The new hair texture remains

unchanged with perampanel dose titration to 6 mg daily. Valproate blood level was 139 mcg/ml before the onset of this side effect.

*Reviewer comments: This case described temporal association between perampanel exposure and onset of hair curling. A robust causality assessment is limited by the concomitant use of valproate, a medication that has been reported to be associated with hair curling in the medical literature.[10,11] To our knowledge, no additional literature reports link hair curling to perampanel. An exploratory search of the FAERS database identified no additional cases of hair curling with perampanel. There is insufficient evidence to support a signal of hair curling with perampanel at this time.*

**FAERS Case#18457687; MCN: US-LUPIN PHARMACEUTICALS INC.-2020-08094:**[12]

- A literature case reported a 3-year-old female patient was treated with perampanel for seizures. Medical history included gene mutation and parental consanguinity. Medication trials including valproic acid, cortisone, levetiracetam, and lacosamide failed to control the seizures. Two days following the initiation of perampanel, the patient experienced motor and speech regression. The patient developed acute-onset imbalance and overall slowed movements and "head drop," and subsequently she stopped ambulating and was unable to sit without assistance. The patient had developmental regression, including speech regression from >10 words to 5-6 words. The patient had been able to stand unassisted and walk distances prior to perampanel initiation. Perampanel was discontinued and the patient regained some function such as sitting, but remained non-ambulatory with poor head control. The patient was then treated with valproic acid, vigabatrin, and lacosamide, during which an electroencephalogram (EEG) revealed generalized spike and wave complexes both in awake and sleep. Magnetic resonance imaging (MRI) of the brain was normal. Gene exome sequencing showed homozygous c.578>A p.(Gly193Asp) missense mutation in the FRRS1L gene and heterozygous c2771C>T p.(Ser924Phe) missense mutation in the ASH1L gene. Levetiracetam, valproic acid, cortisone, and lacosamide were also discontinued. The outcome of developmental regression was not reported.

  *Reviewer comments: The patient's baseline vocabulary is delayed for age,[13] reflecting pre-existing developmental delay. The presence of genetic mutations associated with developmental disorders[14,15] further suggest pre-existing developmental delays. The case reported acute-onset imbalance and abnormal coordination that could contribute to the development regression, particularly regression in ambulation in this case. Perampanel is currently labeled in the WARNINGS AND PRECAUTIONS section for neurologic effects such as disturbance in gait or coordination.[6] A robust causality assessment is limited by the presence of pre-existing developmental disability and the perampanel labeled adverse event experienced by this patient. An exploratory search of the FAERS database identified no additional cases coded with the Preferred Term of Developmental regression with perampanel. There is insufficient evidence to support a signal of developmental regression with perampanel at this time.*

## 4 DISCUSSION

We reviewed all FAERS U.S. serious cases with perampanel in the pediatric population (ages 0 to <17 years) during the period of February 1, 2019, through September 7, 2022. Our evaluation identified one case describing hair curling and one case describing developmental regression; however, there is insufficient evidence to support a new signal at this time.

## 5 CONCLUSION

DPV-I did not identify any new pediatric safety concerns for perampanel at this time.

## 6 RECOMMENDATION

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

## 7 REFERENCES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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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## 8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=2)

| | Initial FDA Received Date | FAERS Case # | Version # | Manufacturer Control # | Case Type | Age (years) | Sex | Country Derived | Serious Outcomes* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 03-NOV-2020 | 18457687 | 1 | US-LUPIN PHARMACEUTICALS INC.-2020-08094 | 15-DAY | 2 | Female | USA | Other |
| 2 | 07-JUL-2020 | 17988482 | 1 | US-LUPIN PHARMACEUTICALS INC.-2019-07866 | PERIODIC | 13 | Female | USA | Other |

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.



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