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

Pediatric Postmarketing Pharmacovigilance Review

Date:	May 3, 2019
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Product Name:	Fycompa (perampanel) oral tablets and suspension
Application Type/Number:	NDA 202834, 208277
Pediatric Labeling Approval Dates:	June 19, 2015 (NDA 202834) April 29, 2016 (NDA 208277) July 26, 2017 (NDA 202834, 208277)
Applicant/Sponsor:	EISAI INC
OSE RCM #:	2019-225

TABLE OF CONTENTS

EXECUTIVE SUMMARY

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

The FDA first approved perampanel on October 22, 2012 for adjunctive therapy for the treatment of partial-onset seizures (POS) with or without secondarily generalized seizures in patients with epilepsy ≥12 years of age. The latest FDA approval occurred on September 27, 2018, which expanded the indication for the treatment of POS, with or without secondarily generalized seizures in patients ≥4 years of age. This review was prompted by the following three labeling changes: 1) June 19, 2015 - expansion of indication to include primary generalized tonic-clonic (PGTC) seizures in patients ≥12 years of age; 2) April 29, 2016 - approval of new oral suspension; and 3) July 26, 2017 - expansion of indication to include monotherapy for POS with or without secondarily generalized seizures in patients with epilepsy ≥12 years of age.

DPV reviewed all FAERS reports with perampanel in the pediatric population (ages 0 - <17 years) during the period February 1, 2015 - January 31, 2019 reporting a serious outcome, and identified 22 cases for discussion. We did not identify new safety signals or an increased severity of labeled adverse events associated with perampanel. The majority of reports described adverse events that were consistent with the known adverse reactions described in labeling or conditions associated with underlying epileptic disease. The reported adverse events were similar for all formulations and ages.

Of the 22 cases evaluated, we identified 1 case describing a fatal event and 1 case describing 2 non-fatal adverse events of interest. The fatal case reported SUDEP and the non-fatal case reported unlabeled events of pancreatitis and urinary retention. In both cases, the patients had multiple risk factors for sudden death and pancreatitis with urinary retention, respectively. The pancreatitis case reported a positive dechallenge and close temporal relationship with perampanel dose increase to support a possible causal association. However, both the fatal and non-fatal cases contained limited information for a more extensive causality assessment. Pancreatitis and cholelithiasis were identified as adverse events of interest at the time of perampanel approval. The singular case of pancreatitis with cholelithiasis identified in this review does not represent a new safety signal at this time, and the Sponsor continues to provide expedited reports and quarterly reports of postmarketing pancreatitis and cholelithiasis events as specified at perampanel initial approval.

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of perampanel, including pancreatitis and urinary retention.

1 INTRODUCTION

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

1.1 PEDIATRIC REGULATORY HISTORY

Perampanel is an antiepileptic drug (AED) that acts as a non-competitive antagonist of the AMPA glutamate receptor on post-synaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS) and is implicated in a number of neurological disorders caused by neuronal over excitation. The precise mechanism by which perampanel exerts its antiepileptic effects in humans is unknown.[1]

Fycompa (perampanel) is available in film-coated tablets (NDA 202834; 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg), and oral suspension (NDA 208277; 0.5 mg/mL).

On October 22, 2012, FDA first approved perampanel oral tablets as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 12 years of age and older.[2] Pancreatitis and cholelithiasis were identified as potential signals with perampanel on initial approval, and FDA requested the Sponsor provide expedited reporting and quarterly reports of postmarketing adverse events of pancreatitis and cholelithiasis.[3]

On December 2, 2013, the U.S. Drug Enforcement Agency (DEA) published a final ruling placing perampanel under Schedule III of the Controlled Substances Act (CSA).[4] On January 2, 2014, perampanel oral tablets became commercially available in the U.S.[5] On April 29, 2016, FDA approved perampanel oral suspension for the same indications.[2]

This review was prompted by three labeling changes, dated June 19, 2015, April 29, 2016, and July 26, 2017. Table 1 summarizes the U.S. approval history of Fycompa (perampanel) and includes information regarding labeling changes to the indication, and the pediatric clinical trials.

Table 1. U.S. Approval History of Fycompa (Perampanel) and Pediatric Clinical Trials[1,2,6]				
Date of Approval	**NDA**	**Indication**	**Pediatric Clinical Trial Information**	**Findings**
10/22/12	202834	Adjunctive therapy for the treatment of partial-onset seizures (POS) with or without secondarily generalized seizures in patients with epilepsy ≥12 years of age	Safety and efficacy in pediatric patients 12 years and older was established by 3 double blind, placebo-controlled studies, which included 72 pediatric patients 12 to 16 years old.	Most common adverse reactions in adult and pediatric patients include dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder.
6/19/15	202834	Treatment of primary generalized tonic-clonic (PGTC) seizures in patients with epilepsy ≥12 years of age	Safety and efficacy in pediatric patients 12 years and older was established by a randomized double-blind, placebo-controlled, multicenter trial, which included 11 pediatric patients 12 to 16 years old; an additional 6 patients were treated with Fycompa in the open label extension of the study.	Adverse reactions were similar to those observed in adults.
4/29/16	208277	Adjunctive therapy for the treatment of POS in patients with epilepsy 12 years of age and older and as adjunctive therapy for the treatment of PGTC seizures in patients with epilepsy ≥12 years of age	Comparable bioavailability of Fycompa oral suspension to Fycompa tablets under steady state established by pharmacokinetic (PK) study intended to demonstrate bioequivalence of 12 mg doses of perampanel given as oral suspension and tablet. Both formulations may be used interchangeably.	No new safety signals observed.

Table 1. U.S. Approval History of Fycompa (Perampanel) and Pediatric Clinical Trials[1,2,6]				
Date of Approval	**NDA**	**Indication**	**Pediatric Clinical Trial Information**	**Findings**
7/26/17	202834 208277	Monotherapy for the treatment of POS with or without secondarily generalized seizures in patients with epilepsy ≥12 years of age	Expansion of indication to include monotherapy for the treatment of POS in patients with epilepsy aged 12 years and older established by PK and pharmacodynamic (PD) studies in POS patients receiving adjunctive perampanel therapy without concomitant enzyme inducing antiepileptic drugs; previously approved for use as adjunctive therapy.	No new safety signals observed.
9/27/18	202834 208277	Treatment of POS, with or without secondarily generalized seizures in patients ≥4 years of age	Expansion of the POS indication to include pediatric patients 4 to < 12 years established by 2 studies in pediatric patients 4 to <12 years of age with epilepsy (total of 225 patients, with 110 patients exposed for at least 6 months, and 21 patients for at least 1 year); previously approved for use in pediatric patients 12 years and older.	Adverse reactions in pediatric patients 4 to <12 years of age were similar to those seen in patients >12 years of age.

The Office of Surveillance and Epidemiology (OSE) previously evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for perampanel in pediatric patients. OSE's evaluation, dated August 3, 2015, was prompted by the labeling changes on October 22, 2012, which was the initial approval of perampanel as adjunctive therapy for the treatment of POS with or without secondarily generalized seizures in patients with epilepsy ≥12 years of age. FDA presented OSE's evaluation to the Pediatric Advisory Committee (PAC) on September 16, 2015. OSE's evaluation did not identify any new safety concerns, and recommended return to routine monitoring for adverse events with perampanel.[7]

1.2 SELECTED LABELED SAFETY INFORMATION

The current approved label for perampanel (September 27, 2018) provides the following information excerpted from pertinent sections:[1]

BOXED WARNING

Serious Psychiatric and Behavioral Reactions

- Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA (5.1)
- Monitor patients for these reactions as well as for changes in mood, behavior, or personality that are not typical for the patient, particularly during the titration period and at higher doses (5.1)
- FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening (5.1)

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)

USE IN SPECIFIC POPULATIONS

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.

Juvenile Animal Data

Oral administration of perampanel (1, 3, 3/10/30 mg/kg/day; high dose increased on postnatal days [PND] 28 and 56) to young rats for 12 weeks starting on PND 7 resulted in reduced body weight, reduced growth, neurobehavioral impairment (water maze performance and auditory startle habituation) at the mid and high doses, and delayed sexual maturation at the high doses. CNS signs (reduced activity, incoordination, excessive grooming/scratching), pup death, decreased hindlimb splay, and decreased hindlimb grip strength were observed at all doses. Effects on pup body weight, pup growth, hindlimb splay, impairment in the water maze performance, and auditory startle persisted after dosing was stopped. A no-effect dose for postnatal developmental toxicity was not identified in this study.

Oral administration of perampanel (1, 5, 5/10 mg/kg/day; high dose increased on PND 56) to juvenile dogs for 33 weeks, starting on PND 42, resulted in CNS signs (incoordination, excessive grooming/licking/scratching, spatial disorientation, and/or ataxic gait) at all doses tested.

2 METHODS AND MATERIALS

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

Table 2. FAERS Search Strategy*	
Date of search	February 5, 2019
Time period of search	February 1, 2015† - January 31, 2019
Search type	FBIS Quick Query
Product terms	Product name: Fycompa Active ingredient: perampanel

* See Appendix A for a description of the FAERS database.
† Data end date of previous OSE Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

3 FAERS RESULTS

3.1 TOTAL NUMBER OF FAERS REPORTS BY AGE

Table 3 presents the number of adult and pediatric FAERS reports from February 1, 2015 - January 31, 2019 with perampanel.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from February 1, 2015 - January 31, 2019 with Perampanel			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥17 years)	793 (171)	693 (89)	62 (6)
Pediatrics (0 - <17 years)	205 (45)	**185‡ (31)**	9‡ (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, and other serious important medical events.
‡ One additional foreign report of pediatric death was identified among reports not reporting an age.

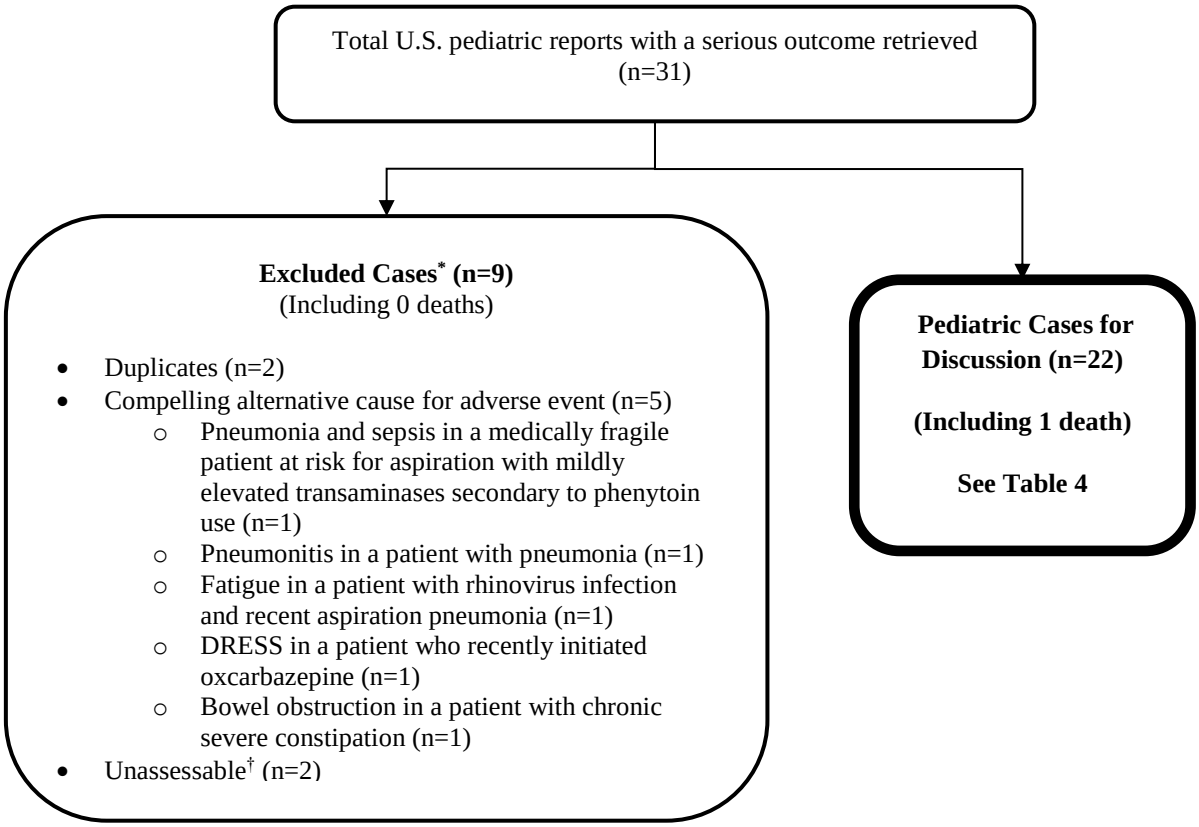
3.2 SELECTION OF U.S. SERIOUS PEDIATRIC CASES IN FAERS

Our FAERS search retrieved 31 U.S. serious pediatric reports from February 1, 2015 - January 31, 2019.

We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded reports from the case series for various reasons, such as if the adverse event (AE) had compelling alternative causes (e.g., the report was confounded by co-morbid diseases or concomitant medications), as well as duplicate or unassessable reports. We included cases with a possible or probable causal association to perampanel. We summarize the remaining cases in the sections below.

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

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



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

† Unassessable: Case cannot be assessed for causality because there is insufficient information reported.

3.3 CHARACTERISTICS OF PEDIATRIC CASES

Table 4 summarizes the 22 FAERS cases in U.S. pediatric patients with perampanel reporting a serious outcome received by FDA from February 1, 2015 - January 31, 2019. Appendix B contains a line listing of the 22 pediatric cases.

Table 4. Characteristics of the FAERS U.S. Serious Pediatric Cases with Perampanel Received by FDA from February 1, 2015 - January 31, 2019 (N=22)

Age	2 - < 6 years	2
	6 - <12 years	7
	12 - < 17 years	13
Sex	Male	8
	Female	14
Formulation	Tablet	12
	Suspension	2
	Unknown	8
Reported reason for use	Epilepsy/seizure NOS	15
	Partial seizures	3
	Generalized seizures	3
	Unknown	1
Serious outcome*	Death	1
	Life-threatening	1
	Hospitalization	16
	Disability	2
	Required intervention	1
	Other serious	12

* 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. A case may have more than one serious outcome. NOS=not other specified

3.4 SUMMARY OF FATAL PEDIATRIC CASES (N=1)

We identified one fatal pediatric adverse event case with perampanel. The case reported sudden unexplained death in epilepsy (SUDEP) with an unlikely causal association to perampanel.

> **FAERS #14125932v3, MCN: US-EISAI MEDICAL RESEARCH-EC-2017-032314, USA 2017:** A 13-year-old female experienced SUDEP 157 days after initiation of perampanel 6 mg daily for the treatment of intractable seizures. Medical history included autism, cerebral palsy, developmental delay, aphasia, diabetes mellitus, and vagal nerve stimulator implantation. Concomitant medications included valproic acid 1125 mg, levetiracetam 1800 mg, and clobazam 17.5 mg (all unknown frequencies). Approximately 2 hours after being placed in her bed to sleep, the patient was found "unresponsive and not breathing." Cardiopulmonary resuscitation was initiated; no seizures were observed during this time. The patient was hospitalized and placed on a ventilator, which was withdrawn because the patient had a "Do Not Resuscitate" order. The cause of death was reported as "brain death asphyxiation" and an autopsy was not performed.

Reviewer comment: This case report is reported with the preferred term "SUDEP" [sudden unexpected death in epilepsy]. SUDEP is defined as "sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning deaths in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, where autopsy examination does not reveal a toxicological or anatomical cause of death." The mechanisms causing SUDEP are unknown, but current evidence suggests a centrally mediated depression of cardiac and respiratory regulation.[8] SUDEP is rare condition with a reported incidence of 1 in 4500 children with epilepsy.[9] It is possible that SUDEP is related to the patient's comorbid conditions as complications from underlying diabetes, intractable epilepsy, or malfunctions from the patient's vagal nerve stimulator are reasonable alternative causes for apnea and sudden death. Additionally, the patient's expressive language delay, inferred from the diagnosis of autism and aphasia, may have contributed to the event in that it precluded her ability to call for help. Causality assessment is difficult with the limited information about the patient's medical conditions and medication evaluation, and in the setting of multiple concomitant medications and long latency between SUDEP and perampanel initiation.

3.5 SUMMARY OF NON-FATAL PEDIATRIC U.S. SERIOUS CASES (N=21)

We identified 21 serious non-fatal FAERS cases with perampanel in the U.S. pediatric population reporting a serious outcome.

The most frequently reported adverse events were consistent with the known adverse reactions described in the labeling. These adverse events are adequately described in the labeling, including the BOXED WARNING, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS sections of the label. No apparent increased severity was observed with these labeled events. Labeled events reported in the 21 cases are listed below.[a]

- Serious psychiatric and behavioral reactions, n=9 (aggression, anger, homicidal ideation, psychotic disorder, hallucination, disorientation)
- Somnolence and fatigue, n=6 (sleepy, lethargic, unresponsive, dysarthria, confusion)
- Dizziness and gait disturbance, n=4 (dizziness, gait instability, weakness, abnormal coordination, vertigo)
- Suicidal behavior and ideation, n=4 (suicide attempt or ideation, overdose)
- Pain, n=2 (extremity, musculoskeletal)
- Weight gain, n=1 (unspecified amount of weight)
- Drug reaction with eosinophilia and systemic symptoms (DRESS), n=1

The serious non-fatal cases reported unlabeled adverse events of pancreatitis, urinary retention, seizures, tremors, and shaking. Pancreatitis and urinary retention are events of interest and will be discussed further in this document. Reported seizures, tremors, and shaking were likely related to patients' underlying epileptic disease. Meaningful causality assessments for these events were limited by the lack of information in the case narratives.

[a] As one case may report more than one adverse event, the number of events is greater than the number of cases.

The reported adverse events were similar for all formulations and ages. There were no observable differences in the distribution and severity of adverse events between perampanel tablet and suspension formulations. Adverse events reported for patients aged <12 years were comparable to those reported for patients aged ≥12 years.

3.6 SUMMARY OF ADVERSE EVENTS OF INTEREST

We identified pancreatitis and urinary retention as unlabeled adverse events of interest in the pediatric population with perampanel. Both adverse events were reported by a singular FAERS case where causal association was possible.

FAERS #13527093v1, Direct report, USA 2017; FAERS # 16163087v1, Direct report, USA 2019: A 14-year-old female experienced pancreatitis and urinary retention 11 days after increasing the dose of perampanel from 2 to 4 mg daily for seizures. Medical history included traumatic brain injury at age 2 years, hydrocephalus treated with ventriculoperitoneal shunt, and epilepsy disorder; there was no history of ketogenic diet, alcohol, or smoking. Concomitant medications included clobazam 15 mg twice daily and 20 mg at bedtime, diazepam 1 mg daily and 2 mg at bedtime, lamotrigine 150 mg daily and 250 mg at bedtime, levetiracetam 1500 mg twice daily, and pyridoxine 25mg daily; the patient had received the same antiepileptic medications for many years.

The patient developed vomiting on day 7 after the perampanel dose increase and was later hospitalized on day 12 with vomiting, diarrhea, fever, increased seizure activity, altered mental status, and urinary retention. Labs on admission (day 12) included elevated lipase of 3319 [U/L] [normal range 25-110 U/L[10]] and serum creatinine (SCr) 0.51 mg/dL (reported as "double baseline value") [normal range 0.42–0.9 mg/dL[11]]. Lipase decreased to 2443 U/L on day 13, and continued to decrease to 957 U/L on day 22. Complete metabolic panels and liver function tests had "a couple abnormal levels (SCr & ALT/AST) but nothing drastic." Cholesterol panel and CBC [complete blood count] was "ok," and ESR [erythrocyte sedimentation rate] and CRP [C-reactive protein] were "elevated, which resolved."

Ultrasound of the liver showed "cholelithiasis (not acute), borderline splenomegaly." CT of the abdomen/pelvis showed "mesenteric fat stranding adjacent to pancreas (can be seen w/ acute pancreatitis), but no CT findings to suggest complications of pancreatitis" and small amount of "free fluid adjacent to right lobe of liver & right paracolic gutter." MRI of the abdomen showed "chronic cholelithiasis w/ dilated cystic duct containing numerous small impacted stones, no filling defects in common bile duct, mild edema in pancreatic body & tail, consistent with acute edematous pancreatitis, no surrounding fluid collections."

The reporter noted the patient had "possible infection (with viral gastroenteritis?) & possibly dehydrated upon admission." The reporter also noted that the urinary retention "may have been due to the dehydration from vomiting/diarrhea & fever & not eating/drinking well due to decreased mentation, etc." and the patient may have "got dehydrated and had a hypoxic hit to her kidneys & liver."

Perampanel was decreased on admission to 2 mg for 4 days, then discontinued; all concomitant antiepileptic medications were continued throughout the admission. The patient remained hospitalized for 1 week after perampanel discontinuation. The patient got "back to baseline," and the events of pancreatitis and urinary retention were resolved.

Reviewer comment: The case reports a plausible temporal relationship to perampanel dose increase and a positive dechallenge. Pancreatitis and cholelithiasis were identified as potential signals at initial drug approval and the Sponsor provides expedited reports and quarterly reports of these postmarketing adverse events as delineated in the Fycompa approval letter.[3] *There are contributory factors that affect the causality assessment. The case also reports chronic cholelithiasis, which is a common cause of acute pancreatitis. Additionally, the patient received two concomitant medications labeled for pancreatitis (lamotrigine, levetiracetam), however, the patient received these medications for "years" and they were continued during the hospitalization with event resolution. In the absence of additional information, the reported urinary retention and elevation from baseline SCr are reasonably attributed to dehydration from possible gastroenteritis in the setting of decreased oral intake.*

4 DISCUSSION

We reviewed all FAERS reports with perampanel in the pediatric population (ages 0 - <17 years) during the period February 1, 2015 - January 31, 2019 reporting a serious outcome, and identified 22 cases for further evaluation. We did not identify new safety signals or an increased severity of labeled adverse events associated with perampanel. The majority of reports described adverse events that were consistent with the known adverse reactions described in labeling or conditions associated with underlying epileptic disease. The reported adverse events were similar for all formulations and ages.

Of the 22 cases evaluated, we identified 1 case describing a fatal event and 1 case describing 2 non-fatal adverse events of interest. The fatal case reported SUDEP and the non-fatal case reported unlabeled events of pancreatitis and urinary retention. In both cases, the patients had multiple risk factors for sudden death and pancreatitis with urinary retention, respectively. The pancreatitis and cholelithiasis case reported a positive dechallenge and close temporal relationship with perampanel dose increase to support a possible causal association. However, both the fatal and non-fatal cases contained limited information for a more extensive causality assessment. Pancreatitis and cholelithiasis were identified as adverse events of interest at the time of perampanel approval. The singular case of pancreatitis with cholelithiasis identified in this review does not represent a new safety signal at this time, and the Sponsor continues to provide expedited reports and quarterly reports of postmarketing pancreatitis and cholelithiasis events as specified at perampanel initial approval.[3]

5 CONCLUSION

DPV did not identify any previously unrecognized pediatric safety concerns for perampanel.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of perampanel, including pancreatitis and urinary retention.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=22)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	8/30/2018	15334993	1	US-MYLANLABS-2018M1064343	Expedited	2	M	USA	HO,OT
2	6/1/2015	11157179	1		Direct	3.7	F	USA	DS,RI
3	3/1/2016	12133968	1	PHEH2016US004476	Non- Expedited	7	F	USA	OT
4	7/14/2016	12559847	1		Direct	7	F	USA	HO,OT
5	4/20/2016	12287048	2	US-EISAI MEDICAL RESEARCH-EC-2016-015969	Non- Expedited	8	M	USA	OT
6	11/16/2017	14194835	4	US-EISAI MEDICAL RESEARCH-EC-2017-033063	Non- Expedited	8.7	M	USA	HO
7	8/3/2015	11331103	2	US-EISAI MEDICAL RESEARCH-EC-2015-009149	Expedited	10	F	USA	HO
8	8/6/2018	15246032	1	US-EISAI MEDICAL RESEARCH-EC-2018-043405	Non- Expedited	10.7	M	USA	OT
9	3/18/2016	12190314	1	US-EISAI MEDICAL RESEARCH-EC-2016-015202	Non- Expedited	11	M	USA	OT
10	1/7/2019 12/27/2018 12/18/2018	15792915 15767442 15735707	1 1 1	US-AUROBINDO-AUR-APL-2018-064091 US-TEVA-2018-US-992722 US-MYLANLABS-2018M1093805	Expedited	12	F	USA	HO,LT,OT
11	10/25/2017	14125932	3	US-EISAI MEDICAL RESEARCH-EC-2017-032314	Expedited	13	F	USA	DE
12	5/13/2015	11115617	2	US-H14001-15-00659	Expedited	13	F	USA	HO
13	10/6/2016	12820657	2	US-EISAI MEDICAL RESEARCH-EC-2016-020692	Expedited	13.7	F	USA	HO
14	11/10/2016	12930115	1		Direct	14	F	USA	DS,HO,OT
15	5/9/2017 3/4/2019	13527093 16163087	1 1		Direct	14.6	F	USA	HO
16	3/6/2015	10892554	1	US-EISAI MEDICAL RESEARCH-E2007-01084-CLI-US	Non- Expedited	14.7	F	USA	HO,OT
17	4/13/2017	13442511	1		Direct	15	F	USA	HO,LT,OT
18	1/15/2016	11922160	1	US-GLAXOSMITHKLINE-US2016GSK005295	Expedited	15	M	USA	HO,OT
19	8/9/2017	13851173	2	US-EISAI MEDICAL RESEARCH-EC-2017-030086	Non- Expedited	16	F	USA	HO
20	1/30/2018	14460712	1	US-EISAI MEDICAL RESEARCH-EC-2018-035507	Non- Expedited	16	F	USA	HO
21	11/20/2017	14204292	1	US-UCBSA-2017045814	Expedited	16	M	USA	HO,OT
22	11/15/2018	15621221	2	US-EISAI MEDICAL RESEARCH-EC-2018-047448	Non- Expedited	16	M	USA	HO

*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, or a congenital anomaly/birth defect, and other serious important medical events. A case may have more than one serious outcome.
DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, OT=Other medically significant, RI=Required intervention, F=female, M=male

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KAREN M LONG
05/03/2019 12:51:58 PM

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05/03/2019 02:20:52 PM

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