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

Date:	June 24, 2019
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Product Name:	Cerebyx® (fosphenytoin sodium)
Pediatric Labeling Approval Date:	March 1, 2017
Application Type/Number:	NDA 020450
Applicant/Sponsor:	Parke-Davis, A Division of Pfizer, Inc.
OSE RCM #:	2019-879

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for fosphenytoin in pediatric patients from birth through age less than 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 fosphenytoin in pediatric patients from March 1, 2016 (one year prior to approval date of pediatric labeling) to April 23, 2019.

FDA approved fosphenytoin on August 5, 1996 and it is indicated for the treatment of generalized tonic-clonic status epilepticus, prevention and treatment of seizures occurring during neurosurgery, and short-term substitution for oral phenytoin when oral phenytoin administration is not possible. FDA approved fosphenytoin on March 1, 2017 for pediatric patients aged less than 17 years for the treatment of generalized tonic-clonic status epilepticus, prevention and treatment of seizures occurring during neurosurgery, and short-term substitution for oral phenytoin when oral phenytoin administration is not possible.

DPV reviewed the serious unlabeled U.S. FAERS reports with fosphenytoin in the pediatric population from birth through age less than 17 years received by FDA from March 1, 2016 to April 23, 2019 and included three cases in our case series. Of these cases, there were no fatalities; the three non-fatal cases described the following unlabeled adverse events, gastric ulcer (n=1) and necrotizing enterocolitis (NEC)(n=2). The case of gastric ulcer provided limited information and described a patient with multiple risk factors for gastric ulcer formation. The remaining two cases were derived from a published case series and described the development of NEC in infants with risk factors for NEC including prematurity and intra-abdominal infection. Further exploration of NEC as an adverse event of interest for fosphenytoin in all age groups in FAERS yielded one additional case report, which originated from the same literature case series. In all three cases, the presence of risk factors for NEC preclude our ability to establish a causal association with fosphenytoin or topiramate, which are both unlabeled for NEC. Additionally, DPV further evaluated NEC with topiramate and determined there was insufficient evidence to indicate a safety issue at this time.

The pediatric safety profile described in the FAERS cases is consistent with the known safety profile and the current fosphenytoin label. DPV did not identify any new pediatric safety concerns. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of fosphenytoin.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for fosphenytoin in pediatric patients from birth through age less than 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 fosphenytoin in pediatric patients from March 1, 2016 (one year prior to approval date of pediatric labeling) to April 23, 2019.

1.1 PEDIATRIC REGULATORY HISTORY

FDA approved fosphenytoin on August 5, 1996 and it is indicated for the treatment of generalized tonic-clonic status epilepticus, prevention and treatment of seizures occurring during neurosurgery, and short-term substitution for oral phenytoin when oral phenytoin administration is not possible.[1] On December 21, 1998, the sponsor submitted a supplemental application for pediatric labeling with data from a Phase 4 post-marketing commitment pediatric pharmacokinetics and safety study.[2] The agency issued a Complete Response letter dated October 21, 1999 on the basis of insufficient information to establish dosing recommendations for the safe and effective use of fosphenytoin in the pediatric population.[2] On September 1, 2016, the sponsor resubmitted a pediatric labeling supplement for the use of fosphenytoin in children.[3] FDA approved fosphenytoin on March 1, 2017 for pediatric patients aged less than 17 years for the treatment of generalized tonic-clonic status epilepticus, prevention and treatment of seizures occurring during neurosurgery, and short-term substitution for oral phenytoin when oral phenytoin administration is not possible.[3]

Fosphenytoin is supplied as a 50mg phenytoin sodium equivalents (PE)/mL injection in two dosage forms:[1]

- 10mL single-dose vials, each containing 500mg PE
- 2mL single-dose vials, each containing 100mg PE

This review was triggered by the sponsor's supplemental application to extend the age range for the currently approved indications to include pediatric patients from birth to age less than 17 years.[3] DPV has not presented fosphenytoin before the Pediatric Advisory Committee.

1.2 DIVISION OF NEUROLOGY PRODUCTS (DNP) CLINICAL REVIEW

DNP evaluated the safety profile of fosphenytoin in the clinical review dated February 9, 2017 for the proposed indications of pediatric generalized tonic clonic status epilepticus, seizures during pediatric neurosurgery, and the short-term substitution for oral phenytoin in pediatric patients.[4] Review of the safety data from 133 pediatric subjects in seven clinical studies and postmarketing safety issues of interest indicated that fosphenytoin is generally safe and well-tolerated in pediatric patients.[4] The clinical studies supporting the use of fosphenytoin in the pediatric population are summarized in **Appendix A**. DNP's review of pediatric postmarketing reports and a comparison of pediatric and adult postmarketing adverse event ratios did not identify any new safety signals.[4] However, DNP noted that an area of potential concern was medication errors and overdose, for which the most frequently reported reasons were incorrect

dose administered, dose calculation error, and product label confusion.[2,4] Therefore, in an effort to reduce medication errors, the agency requested the inclusion of pediatric dosing in the labeling and enhanced pharmacovigilance in the form of quarterly reports for overdoses resulting from medication errors.[2,3]

1.3 RELEVANT LABELED SAFETY INFORMATION[1]

----------BOXED WARNING ----------

WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH RAPID INFUSION RATES

See full prescribing information for complete boxed warning.

- The rate of intravenous CEREBYX administration should not exceed 150 mg phenytoin sodium equivalents (PE) per minute in adults and 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower) in pediatric patients because of the risk of severe hypotension and cardiac arrhythmias.
- Careful cardiac monitoring is needed during and after administering intravenous CEREBYX.
- Reduction in rate of administration or discontinuation of dosing may be needed (2.3, 2.4, 5.2).

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

- Hypersensitivity to CEREBYX, its ingredients, phenytoin, hydantoins (4)
- Sinus bradycardia, sino-atrial block, second and third degree A-V block, and Adams-Stokes syndrome (4)
- A history of prior acute hepatotoxicity attributable to CEREBYX or phenytoin (4, 5.7)
- Coadministration with delavirdine (4)

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

- Dosing Errors: Do not confuse the amount of drug to be given in PE with the concentration of the drug in the vial. Ensure the appropriate volume is withdrawn from the vial when preparing for administration. (5.1)
- Withdrawal Precipitated Seizure: May precipitate status epilepticus. Dose reductions or discontinuation should be done gradually. (5.3)
- Serious Dermatologic Reactions: Discontinue at the first sign of a rash, unless clearly not drug-related. If signs or symptoms suggest SJS/TEN, CEREBYX should not be resumed; consider alternative therapy. (5.4)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity: If signs or symptoms of hypersensitivity are present, evaluate the patient immediately. Discontinue if an alternative etiology cannot be established. (5.5)
- Hematopoietic Complications: If occurs, follow-up observation is indicated and an alternative antiepileptic treatment should be used. (5.8)

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

- Pediatric Use: CEREBYX is indicated for the treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery in all pediatric age groups [see Indications and Usage (1) and Dosage and

Administration (2.3, 2.4)]. Because rapid intravenous administration of CEREBYX increases the risk of adverse cardiovascular reactions, the rate of administration should not exceed 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower) in pediatric patients [see Dosage and Administration (2.3, 2.4) and Warnings and Precautions (5.2)].

- Pregnancy: Phenytoin (the active metabolite of CEREBYX) prenatal exposure may increase risks for congenital malformations and other adverse developmental outcomes (5.14, 8.1)
- Renal and/or Hepatic Impairment or Hypoalbuminemia: Monitor unbound phenytoin concentrations in these patients (8.6)

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

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

Table 1. FAERS Search Strategy*	
Date of Search	April 24, 2019
Time Period of Search	March 1, 2016† - April 23, 2019
Search Type	FBIS Quick Query
Product Terms	Product Active Ingredient: fosphenytoin, fosphenytoin sodium, fosphenytoin sodium heptahydrate
MedDRA Search Terms (Version 22)	All Preferred Terms (PT)
Age (years)	0-16.99
* See **Appendix B** for a description of the FAERS database. † One year prior to approval date of pediatric labeling.	

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 with fosphenytoin from March 1, 2016 to April 23, 2019.

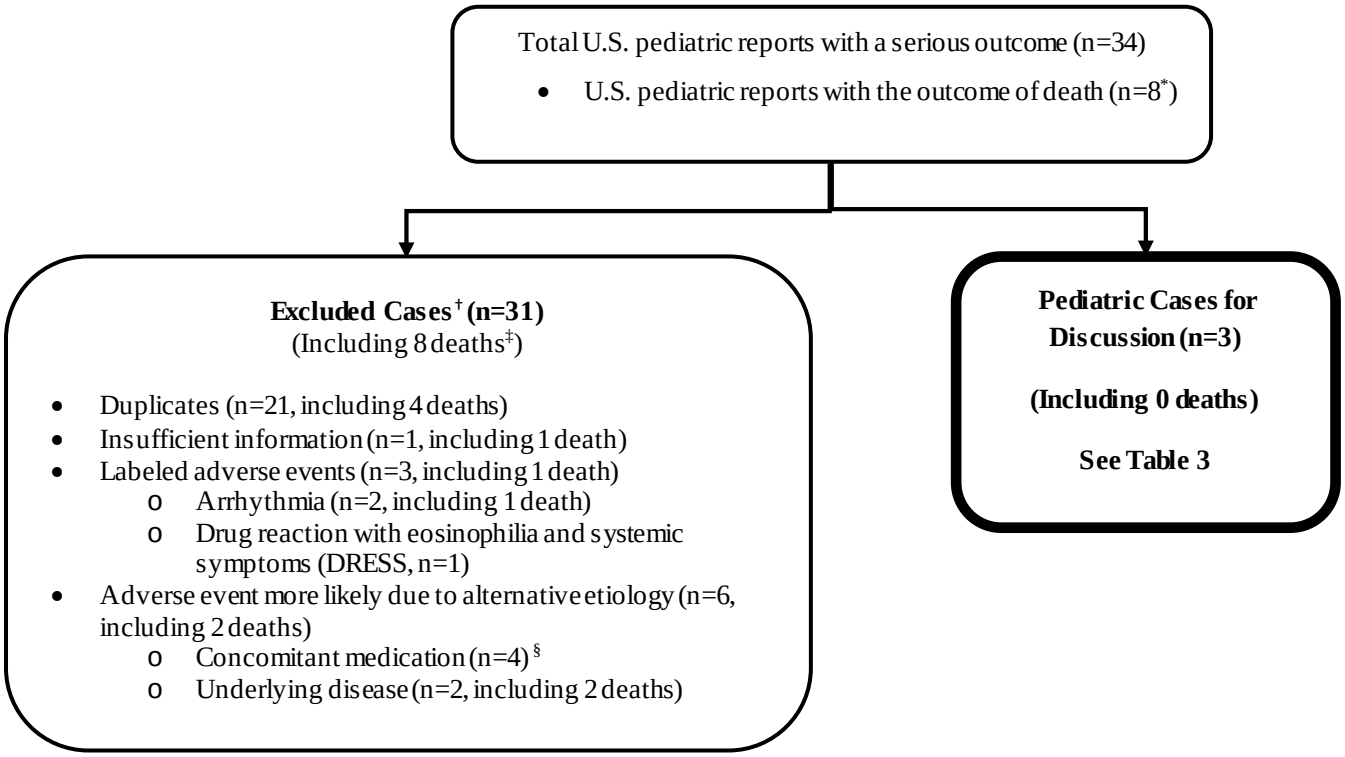
Table 2. Total Adult and Pediatric FAERS Reports Received by FDA from March 1, 2016 to April 23, 2019 with Fosphenytoin*			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	216 (57)	201 (53)	45 (13)
Pediatrics (0 - <17 years)	62 (36)	57 (34)	9 (8)
* May include duplicates 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.			

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

We reviewed all 34 U.S. FAERS pediatric reports with a serious outcome, received by FDA between March 1, 2016 and April 23, 2019. We excluded cases if the case was a duplicate, had insufficient information for analysis, described labeled adverse events, or if the adverse event was more likely due to alternative etiologies. 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 Fosphenytoin



* Eight reports had fatal outcomes; however, four of these reports were duplicates.

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

‡ All cases with a fatal outcome were reviewed and excluded from our case series. Four cases were duplicates; one case lacked information and described an infant with "toxicity to various agents" who suffered brain death; one case described the labeled event of cardiac arrest in an infant in the setting of nonspecific "overdose"; two cases described patients whose underlying diseases, meningoencephalitits and super-refractory myoclonic status epilepticus, respectively, led to fatal outcomes.

§ Adverse events attributed to concomitant medications included: valproic acid-induced hyperammonemic encephalopathy, drug interaction whereby phenobarbital reduced quinidine serum levels that lead to refractory seizures, propylene glycol toxicity following administration of pentobarbital and lorazepam, and levetiracetam-induced behavioral abnormalities.

3.1.3 Characteristics of Pediatric Cases

Appendix C contains a line listing of the three pediatric cases.

Table 3 summarizes the three FAERS cases in U.S. pediatric patients with fosphenytoin reporting a serious outcome received by FDA from March 1, 2016 to April 23, 2019.

Table 3. Characteristics of the FAERS U.S. Serious Pediatric Cases with Fosphenytoin Received by FDA from March 1, 2016 to April 23, 2019 (N=3)		
Age	22 days old	1
	3 weeks old	1
	13 years old	1
Sex	Female	2
	Not reported	1
Reported Reason for Use	Seizures	3
Serious Outcome*	Hospitalization	3
	Other Serious	3
* The following outcomes qualify as serious: hospitalization (initial or prolonged) and other serious important medical events. A case may have more than one serious outcome.		

3.1.4 Summary of Fatal Pediatric Cases (N=0)

We did not include any fatal pediatric adverse event cases in our case series.

3.1.5 Summary of All Pediatric U.S. Serious Cases (N=3)

We identified three FAERS cases with fosphenytoin in the U.S. pediatric population reporting a non-fatal serious unlabeled outcome. These events include necrotizing enterocolitis (NEC) and gastric ulcer.

Gastrointestinal disorders (n=3)

- **Gastric ulcer (n=1)**

FAERS Case # 14318150, Expedited, FDA Received Date December 22, 2017

A 13-year-old male with Sturge-Weber Syndrome was treated with sirolimus for approximately six months and switched to methylprednisolone for the treatment of migraines. Comorbidities included anxiety disorder, attention deficit/hyperactivity disorder, insomnia, migraine, and seizures. On the same day as the methylprednisolone initiation, the patient experienced a stroke-like episode. Fosphenytoin was initiated for seizures at 20mg/kg followed by a second dose at 10mg/kg, three hours and 20 minutes later. Concomitant medications included ketorolac, levetiracetam, levothyroxine, melatonin, methylphenidate, ondansetron, oxcarbazepine, prochlorperazine, and topiramate. Three days later, the patient was discharged on a five-day prednisone taper and a seven-day phenytoin taper. Nine days after discharge, the patient was hospitalized for anemia with a hemoglobin of 7.3g/dL. He underwent endoscopy and was diagnosed with a gastric ulcer, which was treated with lansoprazole and a blood transfusion. The reporter stated that "we do not believe that fosphenytoin or Dilantin® are suspect drugs for the anemia caused by the gastric ulcer. Fosphenytoin has not been commonly associated with gastric irritation. It is more likely that the combination of the stress of hospitalization and methylprednisolone/prednisone contributed to the formation of a gastric ulcer leading to anemia."

Reviewer's Comments: Fosphenytoin is known to cause gastrointestinal hemorrhage, as labeled under Adverse Reactions[1] but it is not labeled for gastric ulcers. This patient had multiple risk

factors for gastric ulcer formation, including the concomitant use of ketorolac, methylprednisolone/ prednisone, and oxcarbazepine, which are all labeled for peptic ulcer under Boxed Warning, Warnings and Precautions, and Adverse Reactions, respectively.[5,6,7,8] *The case lacks information about the patient's symptoms and baseline laboratory values to indicate whether GI bleed or gastric ulcer preceded phenytoin exposure. Given the potential alternative etiologies and limited information, it is difficult to determine the extent to which a causal association between gastric ulcer formation and fosphenytoin exists.*

- **NEC (n=2)**

FAERS Case # 15237492, Literature, Expedited, FDA Received Date August 3, 2018[9]
A 22-day-old, 24 weeks post-conceptual age (PCA), preterm female was born via cesarean delivery with a birth weight of 0.44 kg with Apgar scores of 3 and 6 at one and five minutes respectively. She had respiratory distress syndrome with dependence on mechanical ventilation, an untreated large patent ductus arteriosus (PDA), systemic hypotension with chronic vasopressor dependence, and an abdominal abscess requiring drainage. Concomitant medications were not reported. At 25 weeks PCA, the patient was admitted to the neonatal intensive care unit with seizure disorder, which was refractory to levetiracetam, phenobarbital, fosphenytoin, and a pyridoxine challenge. Electroencephalogram showed "frequent epileptiform discharges originating from the central brain regions and seizure activity." At 27 weeks PCA, topiramate was initiated. Two days after topiramate initiation, she developed abdominal distention, bloody stools, leukocytosis of 33,000/mL, acidosis (pH of 7.15), C-reactive protein elevation to 12.9 mg/dL, and radiographic evidence of NEC. The authors stated that despite the strong temporal association between topiramate administration and NEC, a recurrence of the patient's previous intra-abdominal infection is also possible. The authors concluded that "in light of the patient's multiple risk factors for NEC, topiramate may only be associated but not causal for the development of NEC."

FAERS Case # 15237895, Literature, Expedited, FDA Received Date August 3, 2018[9]
A premature neonate (gender unspecified) with multiple congenital malformations who was born with intrauterine growth restriction at 36 weeks PCA initially required mechanical ventilation and was found to have a PDA with mitral and tricuspid regurgitation. At 39 weeks PCA, the patient developed seizures refractory to levetiracetam and fosphenytoin. At 40 weeks PCA, oral topiramate was initiated. Six days after topiramate initiation, the infant developed bloody stools and abdominal radiograph revealed diffuse colonic distention and pneumatosis, suggestive of NEC. The infant was changed to no enteral feeds and treated with 10 days of antibiotics, during which topiramate was held and seizures were managed with levetiracetam and phenobarbital. At 43 weeks PCA, topiramate was restarted. Six days after topiramate was restarted, the infant developed diffuse colonic distension and pneumatosis, suggestive of recurrent NEC.

Reviewer's Comments: In both cases, the extent to which fosphenytoin contributed to NEC is unknown. The well-described temporal relationship between adverse events and concomitant topiramate therapy in both cases as well as the positive rechallenge with topiramate in FAERS case # 15237895 imply a contributory role of topiramate with NEC. Additionally, the patients had other risk factors for NEC including prematurity[10] *and a previous intra-abdominal infection (FAERS case # 15237492). For completeness, we performed a broad FAERS search using the PTs "necrotising enterocolitis neonatal," "necrotising colitis," "pneumoperitoneum,"*

"abdominal distention," and "sepsis" with fosphenytoin in all age groups for all time through April 23, 2019. We identified one additional FAERS case of NEC with fosphenytoin, which originated from the same literature case series as FAERS case # 15237492 and FAERS case # 15237895. This case described a preterm infant who developed NEC after receiving topiramate for seizures that were refractory to levetiracetam, phenobarbital, and fosphenytoin.[9]

4 DISCUSSION

We reviewed the serious unlabeled U.S. FAERS reports with fosphenytoin in the pediatric population from birth through age less than 17 years received by FDA from March 1, 2016 to April 23, 2019 and included three cases in our case series. Of these cases, there were no fatalities; three non-fatal cases described the following unlabeled adverse events, gastric ulcer (n=1) and NEC (n=2). The case of gastric ulcer provided limited information and described a patient with multiple risk factors for gastric ulcer formation. The remaining two cases were derived from a published case series and described NEC in infants with risk factors for NEC including prematurity and intra-abdominal infection.[9] Further exploration of NEC as an adverse event of interest for fosphenytoin in all age groups in FAERS yielded one additional case report, which originated from the same literature case series.[9] In all three cases, the presence of risk factors for NEC preclude our ability to establish a causal association with fosphenytoin or topiramate, which are both unlabeled for NEC.[1, 11] Additionally, DPV further evaluated NEC with topiramate and determined there was insufficient evidence to indicate a safety issue at this time.

5 CONCLUSION

The pediatric safety profile described in the FAERS cases is consistent with the known safety profile and the current fosphenytoin label. DPV did not identify any new pediatric safety concerns.

6 RECOMMENDATION

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

7 REFERENCES

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8. Trileptal (oxcarbazepine) [Package insert]. East Hanover, NJ: Novartis Pharmaceutical Corporation; March 2018.

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11. Topamax (topiramate) [Package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; May 2019.

8 APPENDICES

8.1 APPENDIX A. SUMMARY OF FOSPHENYTOIN SAFETY PROFILE IN PEDIATRIC CLINICAL TRIALS

Study Number and Title	Number of Pediatric, Age (Years), Total Number of Subjects	Safety Summary*
982-028 An Open-Label, Safety, Tolerance, and Pharmacokinetic Study of Intravenous and Intramuscular Fosphenytoin (Cerebyx®) in Children	Pediatric N=113 Age 0-16 Total N=113	• AEs mild to moderate in severity, similar across age groups, consistent with labeled events • Deaths (N=1): critically ill preterm neonate due to cardiac arrest • Subjects withdrawn from study due to AE (N=1): preterm neonate with elevated phenytoin levels • No significant changes in vital signs
982-016 An Open-Label, Rate-Escalation, Multicenter Study to Assess Safety, Tolerance, and Pharmacokinetics of IV Administered Fosphenytoin Sodium (CI-982) in the Acute Treatment of Generalized Convulsive Status Epilepticus	Pediatric N=10 Age 5-14 Total N=85	• Majority of AEs mild to moderate in severity • SAEs reported in 15% of subjects • Deaths (N=4) unrelated to fosphenytoin
982-426-038a (982-038) Multicenter, Open-Label Study to Assess the Efficacy and Safety of Fosphenytoin Sodium Administered as a Single Intravenous Dose for the Treatment of Status Epilepticus	Pediatric N=4 Age 1-8 Total N=29	• No SAEs reported in pediatric population (11 SAEs in nine adults) • Deaths: pediatric N=0, adult N=8 (seven unrelated to study drug)
982-014 Open-Label, Multicenter Study of the Safety and Tolerance of Intramuscularly-Administered, Multiple-Dose Fosphenytoin in Hospitalized Neurosurgery Patients	Pediatric N=2 Age 16 Total N=118	• AE profile consistent with that of critically ill neurosurgical population • Pediatric deaths (N=1): cause of death was intracranial hypertension unrelated to fosphenytoin • No significant changes in vital signs
982-015 A Double-Blind, Randomized, Parallel- Group, Multicenter Clinical Study of Tolerance and Safety of Multiple Doses of Intravenously Administered Fosphenytoin Sodium (CI-982) versus Dilantin® Parenteral in Neurosurgery patients	Pediatric N=2 Age 15-16 Total N=116	• AEs similar in both treatment groups • Majority of AEs mild to moderate in severity • Better tolerance of fosphenytoin at injection site compared with phenytoin

982-021 A Double-Blind, Parallel-Group, Single-Dose, Multicenter Study Comparing the Safety and Tolerance of Intravenously Administered Fosphenytoin (CI-982) versus Dilantin® Parenteral in the Treatment of Patients Requiring a Loading Dose of Phenytoin	Pediatric N=1 Age 16 Total N=52	• Similar rate of AEs in both treatment groups • Majority of AEs mild to moderate in severity • Pruritis reported with fosphenytoin but not with phenytoin • Better tolerance of fosphenytoin at injection site compared with phenytoin
982-022 An Open-Label, Multicenter Study Assessing the Safety and Tolerance of an Intramuscularly Administered Loading Dose of Fosphenytoin (CI-982) in Patients Requiring a Loading Dose of Phenytoin	Pediatric N=1 Age 16 Total N=60	• Majority of AEs mild to moderate in severity • Mild injection site irritation • SAE (N=1): adult, unrelated to fosphenytoin
* Neither the adult nor the pediatric clinical development program for fosphenytoin included studies designed to demonstrate efficacy. This is because, after administration, fosphenytoin is completely and rapidly cleaved to phenytoin (the active moiety), which has been approved in the U.S. since 1956 for both pediatric and adult patients for the same three indications. AE=adverse event, SAE=serious adverse event		

8.2 APPENDIX B. 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.

8.3 APPENDIX C. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=3)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age	Sex	Country Derived	Serious Outcomes*
1	12/22/2017	14318150	2	US-WEST-WARD PHARMACEUTICALS CORP-US-H14001-17-05021	Expedited	13 years	Female	USA	HO,OT
2	8/3/2018	15237492	1	US-APOTEX-2018AP018545	Expedited	22 days old	Female	USA	HO,OT
3	8/3/2018	15237895	1	US-APOTEX-2018AP018549	Expedited	3 weeks old	NR	USA	HO,OT

*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. 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.

Abbreviations: HO=Hospitalization, OT=Other medically significant, NR=Not reported

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