CLINICAL REVIEW

Application Type	Pediatric Efficacy Supplement
Application Number(s)	NDA 20450 Suppl 003
Priority or Standard	Standard
Submit Date(s)	September 1, 2016
Received Date(s)	September 1, 2016
PDUFA Goal Date	March 1, 2017
Division / Office	DNP, ODE-1, OND, CDER
Reviewer Name(s)	Philip H. Sheridan, MD
Review Completion Date	February 9, 2017
Established Name	Fosphenytoin Sodium Injection
(Proposed) Trade Name	Cerebyx
Therapeutic Class	Anticonvulsant
Applicant	Parke Davis, a division of Pfizer Inc.
Formulation(s)	100 mg PE per 2 mL vial (50 mg PE per mL); 500 mg PE per 10 mL vial (50 mg PE per mL)
Dosing Regimen	Indication-specific

Indication(s)	(1) Pediatric Generalized Tonic Clonic Status Epilepticus (2) Seizures during Pediatric Neurosurgery (3) Short-term Substitution for Oral Phenytoin for Pediatric Patients
Intended Population(s)	Pediatric Patients (b) (4) (Birth to Age 16 yrs)

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval.

A modification of the proposed pediatric loading dose for status epilepticus is recommended as discussed in section 6 of this review.

A number of editorial changes are also recommended to the sponsor's proposed PLR conversion of labeling. The new labeling text will be attached to the pending approval letter.

Enhanced future pharmacovigilance for medication errors should be considered as discussed under "Medication Errors and Overdosages" in section 8 of this review.

1.2 Risk Benefit Assessment

Although the proposed pediatric use of fosphenytoin includes seizure control during neurosurgery and short-term replacement of oral phenytoin when oral administration is not possible, the major pediatric indication proposed is for pediatric generalized tonic clonic status epilepticus.

Status epilepticus is a serious, often life-threatening, medical emergency. Consequences of this prolonged seizure activity may include cerebral hypoxia, hypoglycemia, progressive acidosis, irreversible brain injury, and death.

The overall treatment approach published by the Neurocritical Care Society in 2012 (Brophy 2012) recommends initial IV treatment with a benzodiazepine. If a second dose of a benzodiazepine fails to control the seizures, the second line treatment is IV treatment with fosphenytoin or phenytoin (and/or another IV antiepileptic drug such as valproate or levetiracetam). The third line treatment, if seizures continue, consists of general anesthesia/pharmacological coma.

Fosphenytoin has been widely used for status epilepticus in adults and children. Although it is not currently approved for use in children in the United States, fosphenytoin has been approved for adult use in the United States since 1996, has been extensively used off-label in pediatric patients of all ages in the United States, and is currently approved for pediatric use in the European Union in children aged 5 years and older.

Fosphenytoin was developed as an alternative to parenteral phenytoin. No therapeutic claims for fosphenytoin are made in this submission beyond those approved for parenteral phenytoin in 1956. The clinical development program for fosphenytoin did not include studies designed to specifically demonstrate efficacy.

Fosphenytoin is a prodrug for phenytoin. Upon administration, fosphenytoin is completely converted to phenytoin. As discussed in section 2.1 of this review, fosphenytoin has the therapeutic advantage of having less potential for causing local venous and tissue damage at the injection site. The ability to safely use smaller veins for the administration of fosphenytoin IV (as compared to phenytoin IV) could be a significant factor in emergency and routine care of epileptic patients requiring parenteral medications. This might be particularly relevant in children, in whom the maintenance of venous access in an emergency situation often represents an additional challenge. Due to rapid conversion to phenytoin in the body, fosphenytoin may be used in all clinical situations that require parenteral phenytoin as an anticonvulsant.

In this submission, Modeling and Simulation (as discussed in section 6 of this review) provides the basis for the proposal for administration of fosphenytoin (both loading and maintenance doses) in pediatric subjects with ages from birth to16 years. As discussed in section 6, patients receiving the more aggressive loading dose this review recommends for status epilepticus must attain an effective peak level of phenytoin within a narrow therapeutic time window; these patients are closely and continuously monitored for cardiovascular adverse effects so that the administration of fosphenytoin could be reduced in rate or discontinued if necessary. A less aggressive loading dose and rate is recommended for the patients receiving a nonemergent loading dose although these patients should also have continuous cardiovascular monitoring.

Safety data from the clinical studies and postmarketing reports presented in this submission (discussed in section 7 of this review) indicate that fosphenytoin is generally safe and well-tolerated in pediatric patients from birth through 16 years of age, supporting the use of fosphenytoin in pediatrics. Special scrutiny was focused on the relatively large loading dose required for the effective treatment of status epilepticus. The loading dose and rate recommended for pediatric stats epilepticus in this review has been shown to be well tolerated without significant cardiovascular adverse effects. The pediatric studies included premature newborns, neonates, infants, children, and adolescents. Safety data included post-marketing data from the off-label use of fosphenytoin all ages of pediatric patients. No age-dependent differences in the safety or PK of fosphenytoin were observed.

Intravenous phenytoin has a long-established safety profile, as does fosphenytoin in adults. A comparison of pediatric and adult clinical study data did not identify clinically significant differences in adverse events between intravenous phenytoin and fosphenytoin.

This combined evidence indicates that the benefit-risk profile of fosphenytoin is favorable in both adult and pediatric patients for the proposed indications.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

The chemical name of fosphenytoin is 5,5-diphenyl-3- [(phosphonooxy) methyl]-2,4-imidazolidinedione disodium salt.

Fosphenytoin is a prodrug of phenytoin. Upon administration, fosphenytoin is completely converted to phenytoin by blood and tissue phosphatases. For every 1 mmol of fosphenytoin administered, 1 mmol of phenytoin is produced. Fosphenytoin concentrations, doses, and IV administration rates are always expressed as phenytoin sodium equivalents (PE). In fact, 1.5 mg of fosphenytoin sodium is equivalent to 1 mg phenytoin sodium and is referred to as 1 mg PE. However, there is no need to perform molecular weight-based adjustments when converting between fosphenytoin and phenytoin sodium doses because fosphenytoin is always prescribed as phenytoin sodium equivalents (PE).

After absorption, fosphenytoin is completely cleaved (conversion half-life, 8 to 15 minutes) to phenytoin. Formulation as a prodrug gives fosphenytoin several therapeutic advantages over phenytoin including a more neutral pH (8.6 to 9) and increased water solubility, decreased potential for local tissue destruction, and a more rapid infusion rate. Comparing maximum infusion rates, fosphenytoin can be administered at less than or equal to 150 mg PE/minute whereas phenytoin must be administered at less than or equal to 50 mg/ minute. As a result of the lower pH compared with parenteral phenytoin (pH 12) and the absence of organic solvents, fosphenytoin reduces the likelihood of injection site and venous complications that may be associated with intravenous phenytoin administration.

Cerebyx was approved for adult use in 1996. Cerebyx is indicated in adults for the control of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery. Cerebyx can also be substituted, short-term, for oral phenytoin. Cerebyx should be used only when oral phenytoin administration is not possible. Cerebyx must not be given orally.

2.2 Tables of Currently Available Treatments for Proposed Indications

The three proposed pediatric indications are the same as the indication currently labeled for adults for fosphenytoin and for both children and adults for phenytoin injection.

Generalized tonic clonic status epilepticus: Several intravenous anticonvulsants have been used in the emergency treatment of generalized tonic clonic status epilepticus in pediatric patients. The most commonly used alternatives to fosphenytoin are shown in the table along with dosages currently recommended by the 2016 American Epilepsy Guideline (Glauser, 2016).

Table 1 Currently Available Antiepileptic Drugs for GTC Status Epilepticus

Drug	Loading Dose for GTC Status Epilepticus
IV phenytoin	20 mg/kg
IV levetiracetam	60 mg/kg
IV valproic acid	40 mg/kg
IV phenobarbital	15 mg/kg

Seizures during Neurosurgery: A similar list of intravenous antiepileptic drugs (with the addition of other drugs such as lamotrigine, topiramate, and zonisamide) is used for treatment of seizures during neurosurgery

Short-term substitution for oral phenytoin: The only alternative to fosphenytoin would be phenytoin injection.

2.3 Availability of Proposed Active Ingredient in the United States

Cerebyx has been marketed in the United States since 1996.

2.4 Important Safety Issues With Consideration to Related Drugs

As discussed above, fosphenytoin is the prodrug for phenytoin. Phenytoin is the active moiety for both phenytoin and fosphenytoin. As presented in section 7 of this review, a comparison of pediatric and adult clinical study data did not identify clinically significant differences in adverse events between intravenous phenytoin and fosphenytoin.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The resubmission of the sNDA is to obtain approval for pediatric use of intravenous (IV) fosphenytoin for the control of generalized tonic-clonic status epilepticus (SE), the prevention and treatment of seizures occurring during neurosurgery, and for short-term substitution for oral phenytoin.

Cerebyx was approved in the US for these same three indications in adults on August 5, 1996. Fosphenytoin is a prodrug of phenytoin and is rapidly and completely converted to phenytoin after dosing.

Pfizer conducted a Phase 4 post-marketing commitment pediatric pharmacokinetics (PK/PD) and safety study (982-028) which was submitted (with data from 16 additional pediatric subjects from 5 other studies that had enrolled children and adults) as Supplement 003 on December 18, 1998. Supplement 003 was subsequently assessed by FDA as providing insufficient evidence to identify a pediatric dosing regimen that could reliably produce safe and effective plasma levels of unbound phenytoin comparable to the unbound phenytoin plasma levels from the approved phenytoin injection dosing. Therefore, Supplement 003 was issued a Complete Response (CR) letter on October 21, 1999.

Since the original pediatric supplement submission (S-003), one additional Pfizer clinical study has been completed (Protocol 982-038; 12 May 2003 which had enrolled 4 additional pediatric subjects.

After considering a variety of additional pediatric study designs and conferring with the FDA, Pfizer proposed and completed a Modeling and Simulation (M&S) approach.

FDA pharmacometrics staff reviewed the planned Modeling and Simulation detailed proposal and provided comment. In October 2013, Pfizer submitted a Type C meeting request and modeling and simulation reports. In January 2014, Pfizer received advice with regard to the modeling and simulation. In April 2014, FDA provided written comment by email concerning the content of the sNDA resubmission. On December 11, 2015, a pre-sNDA meeting was held to discuss the content of this current resubmission.

If approved, this submission will give pediatric indications to match the currently approved adult indications for fosphenytoin (and the currently approved adult and pediatric indications for phenytoin injection). It will also put the labeling into PLR format.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the data and presentation are acceptable.

3.2 Compliance with Good Clinical Practices

These studies were conducted in compliance with Good Clinical Practices. .

3.3 Financial Disclosures

The Sponsor indicates that all studies except Study 982-038 were completed prior to February 2, 1999, the effective date of 21 CFR Part 54 requiring a Financial Disclosure certification. Study 982-038 was not under a U.S. IND and was completed in 2002. The sponsor certifies that they acted with due diligence in 2016 to try to obtain disclosures from the investigators in this study. The sponsor succeeded in obtaining statements from 9 of the 14 investigators that they had no financial interests concerning fosphenytoin. Despite due diligence, the sponsor was unable to obtain statements from the remaining 5 investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

None.

4.1 Chemistry Manufacturing and Controls

No CMC changes to currently marketed product.

4.2 Clinical Microbiology

No changes to currently marketed product.

4.3 Preclinical Pharmacology/Toxicology

No changes from current labeling

4.4 Clinical Pharmacology

No changes from current labeling.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The fosphenytoin pediatric clinical development program includes assessments of PK, infusion/injection tolerability, and safety. As with the adult program, proof-of-efficacy studies were not conducted since fosphenytoin is quickly converted to the approved anticonvulsant phenytoin. To elucidate any age-dependent differences in the safety or PK of fosphenytoin, the pediatric studies included premature newborns, neonates, infants, children, and adolescents, who were classified according to age as follows:

- Neonates: aged from birth to less than 29 days
- Infants: aged from 29 days to less than 2 years
- Children: aged from 2 years to less than 12 years
- Adolescents: aged from 12 years to less than 17 years

The seven studies are listed in Table 2 from the sponsor's Clinical Overview.

Table 2 Fosphenytoin Studies in Pediatric Subjects

Study Number and Title	Study Design	Number of Subjects Adults and Pediatric Age Range (yrs)	Criteria for Evaluations
982-014 Open-Label, Multicenter Study of the Safety and Tolerance of Intramuscularly-Administered, Multiple-Dose Fosphenytoin in Hospitalized Neurosurgery Patients	OL, multiple-dose, safety, tolerance, and PK	Total population: 118 (16-98) Pediatric population: 2 (both 16)	PHT plasma concentration Safety: vital signs, seizure record, neurological and physical exams, clinical laboratory values, AEs, and injection-site evaluations

Study Number and Title	Study Design	Number of Subjects Adults and Pediatric Age Range (yrs)	Criteria for Evaluations
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	DB, multiple-dose, randomized, PG, active-controlled, safety, tolerance, and PK	Total population: 116 (15-89) Pediatric population: 2 (15-16)	PHT plasma concentration Safety: vital signs, seizure record, neurological and physical exams, clinical laboratory values, AEs, and injection-site evaluations
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	OL, safety, tolerance, and PK	Total population: 85 (5-82) Pediatric population: 10 (5-14)	PHT plasma concentration Safety: vital signs, seizure record, neurological and physical exams, clinical laboratory values, AEs, and injection-site evaluations
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	DB, single-dose, active-controlled, PG safety and tolerance	Total population: 52 (16-73) Pediatric population: 1 (16)	Safety: vital signs, seizure record, neurological and physical exams, clinical laboratory values, AEs, and injection-site evaluations
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	OL, single-dose, safety and tolerance	Total population: 60 (16-80) Pediatric population: 1 (16)	Safety: vital signs, neurological and physical exams, clinical laboratory values, AEs, and injection- site evaluations

Study Number and Title	Study Design	Number of Subjects Adults and Pediatric Age Range (yrs)	Criteria for Evaluations
982-028 An Open-Label, Safety, Tolerance, and Pharmacokinetic Study Of Intravenous and Intramuscular Fosphenytoin (Cerebyx®) in Children	OL, PK, safety, and tolerance in pediatric subjects	Total population: 113 (birth-16) Pediatric population: 113 (birth-16) Neonates, n = 21 Infants, n = 33 Children, n = 45 Adolescents, n = 14	Fosphenytoin and PHT plasma concentration Safety: cardiac rhythm, vital signs, neurological and physical exams, clinical laboratory values, AEs, and injection-site evaluations
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	OL safety and efficacy	Total population: 29 (1-82) Pediatric population: 4 (1-8) Aged 1 yr, n = 1 Aged 7 yrs, n = 2 Aged 8 yrs, n - 1	Seizure discontinuation within 20 min of treatment. Seizures during the 3-day follow-up. % of subjects whose treatment failed due to intolerance Secondary efficacy criterion: percentage of subjects presenting at least 1 seizure Safety: vital signs, physical exams, clinical laboratory values, injection site evaluations, and AEs.

a. Study 982-426-038 will hereafter be referred to as Study 982-038.
Abbreviations: AEs = adverse events, CI-982 = fosphenytoin; DB = double blind, OL = open label, PG = parallel group, PK = pharmacokinetics, PHT = phenytoin

Review Strategy

The Modeling and Simulation (M & S) approach was reviewed in a separate review by Michael Bewernitz, Ph.D. of the Office of Clinical Pharmacology. This is briefly summarized in section 6 of this review.

This clinical review centered on safety data (section 7 of this review) and on labeling recommendations concerning pediatric dosing for safe and effective use and on the conversion to PLR format.

5.3 Discussion of Individual Studies/Clinical Trials

See Table 2 in section 5.1 of this review.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The sponsor proposes the same indications for the pediatric age group (birth to age 16 years) that are currently approved for adults:

- Control of generalized tonic-clonic status epilepticus
- Prevention and treatment of seizures occurring during neurosurgery
- Short-term substitution for oral phenytoin.

6.1.1 Methods

Neither the adult nor the current 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). Phenytoin Injection has been approved in the US since 1956 for both pediatric and adult patients for the same three indications now requested for fosphenytoin in pediatric patients.

The Modeling and Simulation (M & S) approach was utilized for the current submission to provide dosing recommendations for fosphenytoin in pediatric subjects across the entire age range.

Dr. Michael Bewernitz of the Office of Clinical Pharmacology is preparing a detailed review of this M & S approach. The remainder of this section is based on the draft of his review that was available as this clinical review was being written.

The objectives of the population PK M & S approach were as follows:

1. To develop a population PK model for both fosphenytoin and phenytoin in pediatric subjects.

2. To identify a reference range for unbound phenytoin peak values (Cmax) for loading dose simulations

3. To conduct a simulation of various doses of fosphenytoin that would aid in the development of pediatric dosing recommendations in pediatric subjects of all age groups (neonate to adolescent).

Developing a Population PK Model for both fosphenytoin and phenytoin in pediatric subjects

A combined population PK model was developed for phenytoin and fosphenytoin in children, which can reliably estimate unbound phenytoin levels. Pharmacokinetics data used for the modeling analyses were comprised of 2 pediatric studies (Study 982-028 and a published study by Ogutu) and a single adult study (Study 982-024).

In adults, fosphenytoin is dosed as the molar equivalent of adult phenytoin doses. Using pharmacokinetic simulations, the Sponsor explored pediatric fosphenytoin doses that are the molar equivalent of approved pediatric phenytoin dosing.. At the request of the Division, the Sponsor focused on unbound phenytoin concentration resulting from fosphenytoin administration.

Identifying a "Reference Range" for Peak Values (Cmax) of Unbound Phenytoin to use in the Pediatric Dose Simulations

Adult data from Study 982-016 were used to identify the reference range for unbound phenytoin Cmax for the loading dose simulations in pediatrics.

Reaching adequate peak plasma concentrations of unbound phenytoin in a rapid manner is essential for treatment of status epilepticus. Adequate plasma levels of unbound phenytoin would allow for sufficient drug to cross the blood-brain barrier and exert its pharmacologic effect. It is also essential that peak plasma levels be safe in subjects. The adverse effects of concern during loading doses are the cardiovascular effects, such as hypotension and cardiac arrhythmias. Therefore, a loading dose should rapidly deliver an adequate Cmax of unbound phenytoin while avoiding high levels to minimize adverse effects.

However, the lower and upper thresholds of peak plasma concentrations of phenytoin are not well-defined. Hence, data from Study 982-016 in adult subjects were utilized to define a reference range of peak concentrations of unbound phenytoin to be used in the simulation of concentration data in pediatric subjects. Observed concentrations from samples collected within 15 minutes of the end of infusion in Study 982-016 in adult subjects were considered adequate for defining a reference range.

Based on these values, a 90% prediction interval (PI) of 0.950 to 7.47 µg/mL was chosen by the sponsor as a reference value.

The sponsor emphasized that this reference range is not being recommended as a target range to achieve in clinical practice but that it represents a reasonable reference range for assessing various doses in pediatric subjects in the simulation exercise.

Modification of the "Reference Range" by Dr. Bewernitz

Dr. Bewernitz modified the reference range for unbound phenytoin Cmax values in Study 982-016 in adults by only using the data from patients who received doses in the approved adult loading dose range of 15 to 20 mg PE/kg. Using this subset of PK data from Study 982-016, and applying the sponsor's method for computing the 90% PI, **Dr. Bewernitz estimated that the reference range should be 1.04 – 8.51 µg/mL**. He noted that while he thinks this range is more appropriate, overall the difference between his reference range and the sponsor's proposed reference range of 0.95 to 7.47 µg/mL is not expected to be clinically significant.

Conducting a simulation of Cmax from various loading doses of fosphenytoin

The final population PK models for fosphenytoin and phenytoin were used to simulate plasma concentration-time data to determine the appropriate loading and initial maintenance doses for fosphenytoin in pediatric subjects. One hundred trials were simulated, with each trial containing 400 subjects (100 for each pediatric age category: neonates, infants, children, and adolescents).

Results

Dr Bewernitz reviewed these simulations and constructed the following table and two figures (from his Clinical Pharmacology review).

Table 3 Loading Dose Predicted Cmax Values by Age and Dose from Cerebyx vs Dilantin

Loading Dose: *Predicted* Cmax values by Age, Dose: Cerebyx, Dilantin

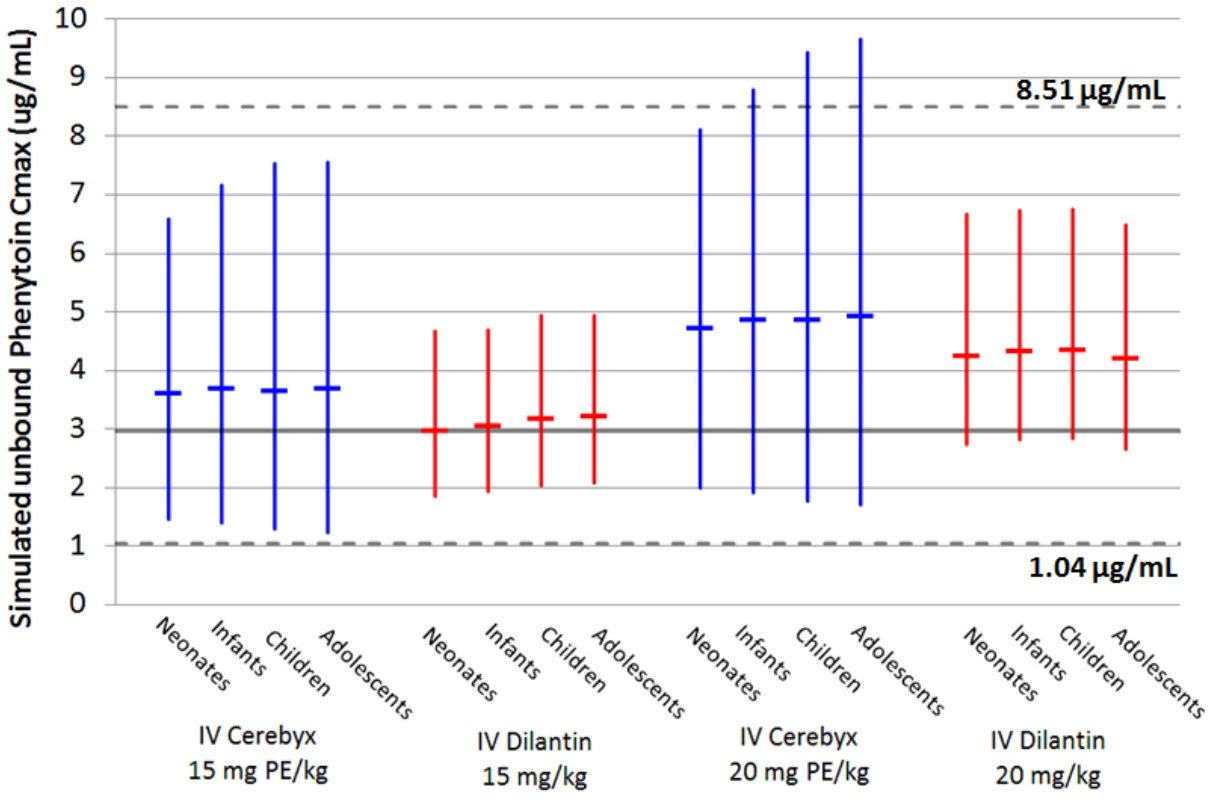
	Age Category	Fosphenytoin Loading Dose	Median (95%CI) of Simulated C_{max} Values of Free Phenytoin (µg/mL)	
			5th percentile	50th percentile	95th percentile
IV Cerebyx Simulations	Neonates	10 mg PE/kg	0.970 (0.640, 1.33)	2.42 (2.03, 2.86)	4.88 (3.83, 6.27)
		15 mg PE/kg	1.47 (0.970, 2.05)	3.60 (3.05, 4.22)	6.58 (5.31, 8.50)
		20 mg PE/kg	1.99 (1.31, 2.82)	4.71 (4.05, 5.58)	8.11 (6.52, 10.1)
	Infants	10 mg PE/kg	0.910 (0.580, 1.34)	2.45 (2.02, 2.90)	5.14 (3.91, 6.31)
		15 mg PE/kg	1.40 (0.880, 2.02)	3.68 (3.04, 4.30)	7.16 (5.64, 8.66)
		20 mg PE/kg	1.91 (1.21, 2.74)	4.85 (4.05, 5.71)	8.80 (7.05, 10.6)
	Children	10 mg PE/kg	0.840 (0.530, 1.30)	2.42 (1.99, 2.88)	5.23 (4.00, 6.81)
		15 mg PE/kg	1.29 (0.810, 1.95)	3.64 (3.01, 4.35)	7.53 (5.85, 9.66)
		20 mg PE/kg	1.76 (1.12, 2.67)	4.86 (4.05, 5.70)	9.44 (7.38, 11.7)
	Adolescents	10 mg PE/kg	0.800 (0.480, 1.24)	2.45 (1.77, 2.92)	5.20 (3.89, 7.60)
		15 mg PE/kg	1.24 (0.760, 1.93)	3.68 (2.70, 4.41)	7.56 (5.68, 11.0)
		20 mg PE/kg	1.70 (1.05, 2.59)	4.92 (3.62, 5.93)	9.65 (7.44, 13.8)
	Age Category	**Phenytoin Loading Dose**	**Median (95%CI) of Simulated C_{max} Values of Free Phenytoin (µg/mL)**	
			5th percentile	**50th percentile**	**95th percentile**
IV Dilantin Simulations	Neonates	15 mg/kg	1.86 (1.51, 2.26)	2.97 (2.66, 3.33)	4.67 (4.06, 5.54)
		17.5 mg/kg	2.34 (1.85, 2.77)	3.64 (3.27, 4.10)	5.73 (4.89, 6.78)
		20 mg/kg	2.73 (2.18, 3.22)	4.24 (3.81, 4.77)	6.68 (5.66, 7.88)
	Infants	15 mg/kg	1.94 (1.51, 2.25)	3.04 (2.73, 3.38)	4.70 (4.09, 5.66)
		17.5 mg/kg	2.41 (1.95, 2.76)	3.68 (3.31, 4.15)	5.80 (4.88, 6.98)
		20 mg/kg	2.82 (2.31, 3.22)	4.33 (3.81, 4.83)	6.73 (5.66, 8.21)
	Children	15 mg/kg	2.04 (1.58, 2.37)	3.16 (2.83, 3.53)	4.94 (4.14, 5.73)
		17.5 mg/kg	2.47 (1.90, 2.86)	3.80 (3.38, 4.22)	5.91 (4.93, 7.03)
		20 mg/kg	2.83 (2.19, 3.27)	4.34 (3.86, 4.84)	6.75 (5.63, 8.08)
	Adolescents	15 mg/kg	2.07 (1.61, 2.39)	3.21 (2.83, 3.55)	4.94 (4.22, 5.86)
		17.5 mg/kg	2.36 (1.85, 2.76)	3.71 (3.28, 4.13)	5.73 (4.89, 6.78)
		20 mg/kg	2.65 (2.09, 3.11)	4.20 (3.73, 4.64)	6.49 (5.53, 7.63)

Each percentile value is expressed as a median of that value across numerous simulations (with certainty of that value presented by the 95% CI, wider CI indicates lower certainty in the percentile value)

The results are simpler to interpret when displayed in the following figure (also from Dr. Bewernitz's review).

Figure 1 Simulated Unbound Phenytoin Cmax Distribution for Pediatric vs. Adult Patients at Proposed Status Epilepticus Loading Dose

Figure 5: Simulated Unbound Phenytoin Cmax Distribution for Pediatric Patients Versus Adults at Proposed Status Epilepticus Loading Dose (15-20 mg PE/kg)



The horizontal grey solid and dashed lines represent the 90% PI (1.04 to 8.51 µg/mL) and median prediction (2.97 µg/mL) for unbound phenytoin C_{max} based on PK data from adults receiving IV Cerebyx doses in the range of 15-20 mg PE/kg in study 982-016. The vertical lines with intersecting horizontal lines represent the 90% PI and median prediction for pediatric patients grouped by age group, dose, and drug (Cerebyx or Dilantin). Blue represents simulated unbound Cmax values following IV Cerebyx administration to virtual pediatric patients and red represents simulated unbound phenytoin Cmax values following IV Dilantin administration to virtual pediatric patients.

Dr. Bewernitz concludes that the appropriate pediatric loading dose for fosphenytoin for status epilepticus for all pediatric age groups (neonates, infants, children, and adolescents) is 15-20 mg PE/kg.

Reviewer's Note:

The table and figure from Dr. Bewernitz indicate that the simulated unbound phenytoin Cmax from the currently approved pediatric loading dose of phenytoin injection for status epilepticus (15-20 mg/kg) is closely approximated by the simulated unbound phenytoin Cmax from a pediatric loading dose of 15-20 mg PE of fosphenytoin. Although there are some predicted phenytoin serum level values that slightly exceed the "reference range" at the 20 mg PE/kg fosphenytoin dosing level, this review discusses the safety data in section 7 of this review which indicate that attaining these higher levels does not pose a significant risk for serious cardiovascular adverse effects.

Status epilepticus is a life-threatening medical emergency. Successful treatment (when initial benzodiazepine therapy does not suffice) demands that an adequate Cmax of phenytoin be attained within a short time period or else the time window for efficacious intervention with intravenous antiepileptic drugs (estimated to be as short as about 1 hour) may close with the result of the status epilepticus becoming refractory and requiring more aggressive therapy with higher risks (i.e., pharmacologic coma with general anesthesia). When the loading dose of fosphenytoin for status epilepticus is given, the patient is being closely and continuously monitored for vital signs and electrocardiography, allowing for slowing or discontinuation of the loading dose in the exceptional patient for whom this dose may be too aggressive. Thus, the risk-benefit for the 15-20 mg PE/kg loading dose for status epilepticus is favorable.

The fact that the 15-20 mg PE/kg dose of fosphenytoin is currently labeled for adults with status epilepticus would mean that the same fosphenytoin dose for status epilepticus would be approved for all ages from neonates to adults. This would be expected to reduce potential errors in dosing. This loading dose also corresponds to the approved pediatric loading dose of IV phenytoin (15-20 mg/kg) for status epilepticus. In addition, both the Neurocritical Care Society (Brophy 2012) and the American Epilepsy Society (Glauser 2016) have recommended a fosphenytoin loading dose of 20 mg PE/kg for status epilepticus for all ages.

Nonemergent loading dose

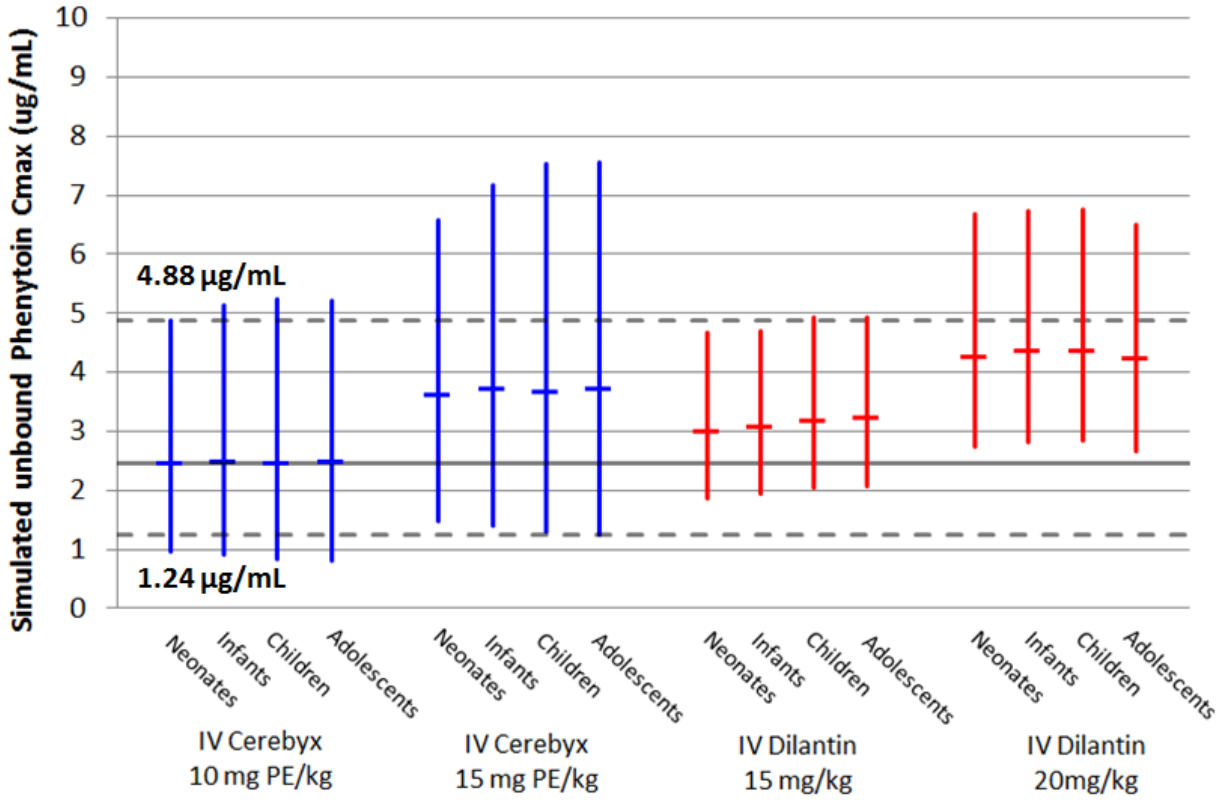
The medical need for treatment of subjects in nonemergent situations is different than those with status epilepticus. In nonemergent situations, a provision to allow for a lower

loading dose seems appropriate. Therefore, for nonemergent situations, a loading dose of fosphenytoin of 10 to 15 mg PE/kg was proposed.

A similar figure was constructed by Dr. Bewernitz which indicates that the simulated unbound phenytoin Cmax from the currently approved pediatric nonemergent loading dose of phenytoin injection (15 mg/kg) is closely approximated by the simulated unbound phenytoin Cmax from a pediatric loading dose of 10-15 mg PE of fosphenytoin.

Figure 2 Simulated Unbound Phenytoin Cmax Distribution for Pediatric vs. Adult Patients at Proposed Cerebyx Loading Dose for Non-Emergent Indications

Figure 6: Simulated Unbound Phenytoin C_{max} Distribution for Pediatric Patients Versus Adults at Proposed Cerebyx Loading Dose for Non-emergent Indications



The horizontal grey solid and dashed lines represent the 90% PI (1.24 – 4.88 µg/mL) and median prediction (2.46 µg/mL) based on PK data from adults receiving IV Cerebyx doses in the range of 10-15 mg PE/kg in study 982-016. The vertical lines with intersecting horizontal lines represent the 90% PI and median prediction for pediatric patients grouped by age group, dose, and drug (Cerebyx or Dilantin). Blue represents simulated unbound Cmax values following IV Cerebyx administration to virtual pediatric patients and red represents simulated unbound phenytoin Cmax values following IV Dilantin administration to virtual pediatric patients.

Maintenance Dose: The Division approved of the sponsor's plan to use the labelled therapeutic range of 1-2 µg/mL as a target for exposure during the maintenance phase. The sponsor provided comparisons of simulated unbound phenytoin Cmax values resulting from virtual pediatric patient's receiving loading and maintenance doses with the target range of 1-2 µg/mL. This resulted in a recommended pediatric initial maintenance dose of 2 -4 mg PE/kg every 12 hours at a rate of 1 -2 mg PE/min (no faster than 100 mg PE/min).

Reviewer Note:

Dr Bewernitz and this reviewer concur that the nonemergent loading dose and maintenance dose recommendations proposed by the sponsor are appropriate.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from 133 pediatric subjects from 7 clinical studies are summarized in Table 4 (the sponsor's Table 7 from Clinical Overview).

The majority of these subjects (n = 113, 85%) were from Study 982-028, an open-label study designed to evaluate the safety, tolerance, and PK of fosphenytoin IV and fosphenytoin IM in pediatric subjects (aged from birth through 16 years), including neonates and infants. Seventy-seven of these subjects were younger than 5 years of age (including 1 subject who entered the study twice). Study 982-028 was conducted to support a pediatric indication in the original pediatric sNDA in 1999. The remaining 20 subjects came from 6 other studies that allowed enrollment of subjects aged 16 years or younger but none of these studies were specifically designed as pediatric studies.

Table 4 Summary of Fosphenytoin Safety Profile in Clinical Studies

Study Number Study Title	Number of Subjects (Total) Number of Pediatric Subjects (age range [yrs])	Safety Summary
982-014 Open-Label, Multicenter Study of the Safety and Tolerance of Intramuscularly Administered, Multiple Dose Fosphenytoin in Hospitalized Neurosurgery Patients	Total N = 118 Pediatric N = 2 (both 16)	AE profile reflects seriously ill neurosurgical subject population: • One or more AEs were experienced by 89 (75%) subjects. • Ten (9%) subjects had treatment-related AEs. • Seven deaths (6 adults; 1 adolescent died due to intracranial hypertension), none related to study drug; all were attributed to underlying conditions (eg, intracranial hemorrhage, IIP) • AEs in ≥10% of subjects were: fever (18%), surgeries/procedures (14%), somnolence (13%), nystagmus (12%), ataxia (12%), and constipation (10%). • Mild irritation at injection site: 3 subjects (2.8%) • No significant changes in vital signs were observed.
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	Total N = 116 Pediatric N = 2 (15-16)	AEs were similar in both treatment groups and were consistent with expectations in this population. • The most frequently reported AEs in the fosphenytoin-treatment group were nystagmus (13.6%), constipation (12.5%) and fever (12.5%) • Majority of AEs were mild-to-moderate in severity • Four subjects (2 in each treatment group) withdrew from study participation due to 1 or more AEs. Of these, 2 died (1 fosphenytoin-treated subject and 1 phenytoin-treated subject); neither death was considered related to study medication. • Fosphenytoin IV was tolerated significantly better at the infusion site (ie, less irritation and injury) than phenytoin IV.

Study Number Study Title	Number of Subjects (Total) Number of Pediatric Subjects (age range [yrs])	Safety Summary
982-016 Open-Label, Rate-Escalation Multicenter Study to Assess Safety, Tolerance, and Pharmacokinetics of Intravenously Administered Fosphenytoin Sodiun (CI-982) in the Acute Treatment of Generalized Convulsive Status Epilepticus	Total N = 85 Pediatric N = 10 (5-14)	AEs were reported in 81% of subjects. • Majority of AEs were mild-to-moderate in severity (severe AEs were reported in 16% of subjects). • Reported AEs, regardless of causality, included nystagmus (27%), agitation (15%), ataxia (14%), headache (12%), pruritus (11%), somnolence (9%), vomiting (8%), and dizziness (7%). • SAEs were reported in 15% of subjects. • Four subjects died after conclusion of the study; none of the deaths were considered related to fosphenytoin.
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	Total N = 52 Pediatric N = 1 (16)	A similar percentage of subjects in each treatment group (92% of fosphenytoin-treated subjects and 85% of phenytoin-treated subjects) experienced at least 1 AE. • Majority of AEs were mild-to-moderate in severity. • Reported AEs in the fosphenytoin-treatment group, regardless of causality, included nystagmus (46%), pruritus (31%), dizziness (26%), ataxia (18%), headache (18%), pain (13%), amblyopia (10%), paresthesia (10%), and vertigo (10%). • Pruritus was experienced by 31% of fosphenytoin-treated subjects and was not reported in any phenytoin-treated subjects. • Fosphenytoin was significantly better tolerated at the infusion site than was phenytoin.

Study Number Study Title	Number of Subjects (Total) Number of Pediatric Subjects (age range [yrs])	Safety Summary
982-022 An Open-Label, Multicenter Study Assessing the Safety and Tolerance of Intramuscularly Administered Loading Dose of Fosphenytoin (CI-982) in Patients Requiring a Loading Dose of Phenytoin	Total N = 60 Pediatric N = 1 (16)	• Majority of AEs were mild-to-moderate in severity • Several days after dosing, 1 subject (adult) experienced the following SAEs: arrhythmia, neuropathy, stupor, and tachycardia. None were considered related to fosphenytoin. • Reported AEs included nystagmus (47%), dizziness (17%), ataxia (13%), incoordination (7%), and tremor (7%). • Three hours after injection, mild injection site irritation was experienced by 3 subjects. • At follow-up (2-7 days post IM dose), 4 subjects (7%) had mild injection site irritation.
982-028 An Open-Label, Safety, Tolerance, and Pharmacokinetics Study of Intravenous and Intramuscular Fosphenytoin (Cerebyx®) in Children.	Total N = 113 Pediatric N = 113 (birth-16) Neonates, n = 21 Infants, n = 33 Children, n = 45 Adolescents, n = 14	• AEs were generally similar across age groups. • Reported AEs were consistent with those expected with fosphenytoin therapy (labeled events) or with the subject's medical condition and/or postoperative status. • Reported AEs in fosphenytoin-treated subjects (all age groups combined and irrespective of causality) included nystagmus (20%), vomiting (19%), ataxia (13%), fever (8%), somnolence (7%) nervousness (6%), and pruritus (5%). • Majority of AEs were mild-to-moderate in severity. • One critically ill, premature, neonate died. This subject was withdrawn due to the SAE of heart arrest. The death was not attributed to study medication. • Another premature neonate was withdrawn due to the AE of phenytoin level increased. This subject recovered. • Fosphenytoin was well-tolerated at the infusion/injection site.

Study Number Study Title	Number of Subjects (Total) Number of Pediatric Subjects (age range [yrs])	Safety Summary
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	Total N = 29 Pediatric N = 4 (1-8)	• At least 1 AE was experienced by 79% of subjects; of these, 46% were considered possibly treatment related. • Commonly reported AEs were injection-site reactions (34%), injection site edema (14%), hypotension (10%), increased sedimentation rate (10%), headache (7%), nausea (7%), leukocytosis (7%), and abdominal pain (7%). • Eleven SAEs were reported in 9 subjects (none in the pediatric population). • 2 adults experienced at least 1 AE leading to discontinuation • Eight deaths (28% of total subjects) were reported. Of these, 2 were during the follow-up period and 6 were after the follow-up period. Seven of 8 deaths were not considered related to study medication and the other (PE) was considered unlikely related to study medication. None were in pediatric subjects.

aavAbbreviations: AE = adverse event, IIP = increased intracranial pressure, IM = intramuscular, IV = intravenous, LD = loading dose, MD = maintenance dose, PE= pulmonary embolism, SAE = serious adverse event

7.2 Adequacy of Safety Assessments

The absence of randomized, double-blind, controlled trials limits the available safety data. However, the clinical study data available, post marketing surveillance, the long-term experience with the active moiety (phenytoin) since 1956, and 20 years of experience with fosphenytoin in adults and (off-label) in children indicate that fosphenytoin can be used safely in the proposed dosages for the proposed pediatric indications.

7.3 Major Safety Results

7.3.1 Deaths

Two pediatric subjects died in the pediatric development studies.

Study 982-014, Center 001, Subject Number 014: This 16-year-old male was admitted to the hospital with severe closed head injury and second degree burns on the back, buttocks, right arm, and left hand as a result of a motor vehicle accident. He was comatose, and his pupils were unequal and nonreactive. He underwent an exploratory laparotomy, and he had a jejunostomy tube and chest tube inserted. The subject received a loading dose of 900 mg fosphenytoin IM, which produced a trough concentration of 10.6 µg/mL. He then received 500 mg of fosphenytoin IM twice daily (BID) for each of the next 3 days, with trough concentrations of 11.2 and 12.8 ug/mL on Days 3 and 4, respectively. The concomitant medications were reported as cimetidine, heparin, isoflurane, verconium bromide, fentanyl, lidocaine, pentobarbital sodium, butorphanol tartrate, dopamine, epinephrine, desmopressin, morphine, acetaminophen, mannitol, and seonbutol. The subject had decreased hematocrit, hemoglobin, and platelet counts. He developed an uncontrolled rise in intracranial pressure and hypotension. According to the investigators, these events were not related to the study drug. The subject died on Day 5 as a result of herniation of the brain following this severe rise in intracranial pressure (ICP).

Reviewer Note:

This patient died as a result of brain herniation following severe closed head trauma independent of any effect from fosphenytoin.

Study 982-028, Center 004, Subject Number 007: This 11-day-old (premature neonate) female with neonatal SE was hospitalized for Escherichia coli sepsis and meningitis and subsequently died due to cardiac arrest on Study Day 1. The subject had a history of patent ductus arteriosus, intraventricular hemorrhage, and thrombocyto-penia due to disseminated intravascular coagulation disorder, hypotension, bradycardia, respiratory distress syndrome with interstitial emphysema. The subject received a loading dose of 22.00 mg (24.44 mg PE/kg) fosphenytoin IV, which was infused at a rate of 1.63 mg/kg/min for continuing seizures. The unbound phenytoin level measured 3.42 minutes after the IV loading dose was administered on Study Day 1 was reported as 14.4 µg/mL. Concomitant medications included dopamine, dobutamine, phenobarbital, lorazepam, fentanyl, cefotaxime, tobramycin, clindamycin, and vancomycin. Prior to the infusion of the study medication, the subject was hemodynamically unstable, with a blood pressure of 31/19 mm Hg and a heart rate of

147 beats per minute (bpm), and was receiving maximum medical support. During the infusion of study medication, the subject's hemodynamic status continued to decline. Approximately 10 minutes after the infusion was complete, the subject went into cardiopulmonary arrest and died. The investigator considered this event definitely unrelated to fosphenytoin.

Reviewer Note:

This premature neonate had many life-threatening conditions including pre-existing hemodynamic instability, sepsis, disseminated intravascular coagulation, and intraventricular hemorrhage. These critical illnesses may have distorted the pharmacokinetics of unbound phenytoin (e.g., reduced protein binding) She received a relatively high loading dose (24.44 mgPE/kg) above the dosage of 15-20 mgPE/kg this reviewer is proposing for status epilepticus and the level of phenytoin (presumably at or near Cmax) was 14.4 ug/ml which is above the level predicted by the modeling simulations for a loading dose of 15-20 mgPE/kg. The concomitant phenobarbital may have raised the phenytoin level (a potential interaction noted in the currently approved Cerebyx labeling).

7.3.2 Nonfatal Serious Adverse Events

None.

Both of the two patients who experienced SAEs died. They are discussed in section 7.3.1 of this review.

7.3.3 Dropouts and/or Discontinuations

Three patients were withdrawn from study participation due to AEs.

In the 7 clinical studies comprising this submission, 5 of the 133 patients (3.8%) fosphenytoin-treated pediatric subjects were withdrawn. Two subjects were withdrawn because of administrative reasons (lost to follow-up). The remaining 3 subjects (2.3%) were withdrawn due to 1 or more AEs occurring during fosphenytoin treatment. Of these, 2 were withdrawn due to fatal SAEs (as described in section 7.3.1). The remaining subject (Study 982-028, Center 005, Subject 009) was a 5-day-old premature neonate who experienced elevated plasma phenytoin concentrations on Day 5, which led to withdrawal from the study and discontinuation of fosphenytoin treatment. The subject recovered by study close-out. Her narrative is as follows.

Study 982-028, Center 005, Subject Number 009: This 1-day-old (premature neonate) white female entered the study with a history of possible sepsis and hypotension, and was suffering from respiratory distress syndrome, insulin-dependent diabetes mellitus, acute perinatal anemia, oliguria, patient ductus arteriosus, and hypoxic ischemic encephalopathy. The subject received an IV loading dose of 50.0 mg (15.63 mg/kg) fosphenytoin infused at a rate of 3.021 mg/kg/min for seizures. The subject received two IV maintenance administrations of 2.56 mg/kg fosphenytoin on Study Days 2 and 3, and one IV maintenance administration of 2.56 mg/kg fosphenytoin on Study Day 4. Phenytoin concentration measured 38.3 µg/mL at 05:30 AM on Study Day 5 (21 hours after the end of the most recent maintenance dose) and 1 additional fosphenytoin maintenance dose (2.56 mg/kg) was given before the elevated phenytoin concentration was known. Phenytoin concentration increased to 48.2 µg/mL, fosphenytoin was discontinued, and the subject was withdrawn from the study on Study Day 5. Concomitant medications included acyclovir, caffeine, furosemide, phenobarbital, dopamine, and heparin. No AEs occurred in conjunction with the elevated unbound phenytoin levels. The subject recovered by study closeout. The adverse event of elevated unbound phenytoin was considered nonserious, mild in intensity, and related to study drug.

7.3.4 Significant Adverse Events

Approximately two-thirds of the 133 pediatric subjects experienced at least 1 adverse event and approximately 40% of subjects experienced at least 1 adverse event considered possibly associated with the study medication. Most events were mild-to-moderate in severity. Two subjects experienced serious adverse events (SAEs), both of which resulted in death. None of the serious adverse events were considered related to study drug.

The most frequently reported adverse events in pediatric subjects were similar to those in adults. Specifically, adverse events reported in at least 5% of subjects in the pediatric subjects were nystagmus, vomiting, ataxia, fever, somnolence, nervousness, and pruritus.

Study 982-028 was the largest study in the pediatric program (N=113), enrolling 85% of the total number of pediatric subjects. It was also the only study to enroll subjects in all 4 pediatric age categories. Seventy-two of the 113 (64%) pediatric subjects in Study 982-028 experienced at least 1 adverse event shown in Table 5 (Sponsor's Table 12 from Clinical Overview). Forty percent of the subjects experienced at least 1 adverse event that was considered possibly related to study drug. Within all age groups, a higher percentage of adverse events were reported in female subjects than in male subjects. In all age groups, most events were of mild-to- moderate intensity.

Table 5 Overview of Adverse Events in Study 982-028

	Neonates N = 21 n (%)	Infants N = 33 n (%)	Children N = 45 n (%)	Adolescents N = 14 n (%)	Total N = 113 n (%)
Subjects With ≥ 1 AE	11 (52.4)	23 (69.7)	27 (60.0)	11 (78.6)	72 (63.7)
Subjects With ≥ 1 Treatment-Related AE[a]	4 (19.0)	14 (42.4)	18 (40.0)	9 (64.3)	45 (39.8)
Number of AEs	20	62	84	33	199
Number of Treatment-related AEs	5	28	45	20	98
Subjects With ≥ 1 AE by Sex					
Male	4 (44.4)	14 (63.6)	12 (50.0)	5 (62.5)	35 (55.6)
Female	7 (58.3)	9 (81.8)	15 (71.4)	6 (100.0)	37 (74.0)
Subjects With ≥ 1 Treatment-Related AE by Sex					
Male	1 (11.1)	8 (36.4)	7 (29.2)	4 (50.0)	20 (31.7)
Female	3 (25.0)	6 (54.5)	11 (52.4)	5 (83.3)	25 (50.0)
Subjects With ≥ 1 AE by Race					
White	4 (40.0)	11 (68.8)	13 (59.1)	5 (100.0)	33 (62.3)
Black	3 (60.0)	6 (66.7)	10 (62.5)	5 (71.4)	24 (64.9)
Other	4 (66.7)	6 (75.0)	4 (57.1)	1 (50.0)	15 (65.2)
Subjects With ≥ 1 Treatment-Related AE by Race					
White	3 (30.0)	5 (31.3)	9 (40.9)	3 (60.0)	20 (37.7)
Black	1 (20.0)	4 (44.4)	6 (37.5)	5 (71.4)	16 (43.2)
Other	0 (0.0)	5 (62.5)	3 (42.9)	1 (50.0)	9 (39.1)
Subjects With ≥ 1 AE by Maximum Severity					
Mild	8 (38.1)	14 (42.4)	17 (37.8)	9 (64.3)	48 (42.5)
Moderate	0 (0.0)	9 (27.3)	10 (22.2)	2 (14.3)	21 (18/6)
Severe	3 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)
Subjects With ≥ 1 Treatment-Related AE by Maximum Severity					
Mild	4 (19.0)	12 (36.4)	12 (26.7)	8 (57.1)	36 (31.9)
Moderate	0 (0.0)	2 (6.1)	6 (13.3)	1 (7.1)	9 (8.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths[b]	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
SAEs[b]	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Did not complete study due to ≥ 1 AE	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)

a. An AE was considered treatment-related if the investigator deemed it to be definitely, probably, or

possibly related to the study medication or if there were insufficient information to determine a relationship. b. The death and SAE occurred in the same subject.
Abbreviations: AE = adverse event, n = number of evaluable subjects; N = total number of subjects; SAE = serious adverse event
Source: CSR 982-028 Table 11 (also Parke-Davis Clinical Data Summary of Fosphenytoin Therapy in Pediatric Patients, Section 3.2.3.1, Table 7)

Adverse events reported in 2% or more of subjects in Study 982-028 are listed in Table 6 (from the sponsor's Table 13 in Clinical Overview) by total number and by number of treatment-related AEs. The types of AEs reported during the study were similar across all 4 pediatric age groups. Adolescent subjects had the highest percent of AEs and treatment-related AEs (79% and 64%, respectively) and neonates experienced the lowest percent of AEs and treatment-related AEs (52% and 19%, respectively). The greatest number of AEs was reported in the (Central) Nervous System body system. The most frequently reported AEs (all causes) were nystagmus, vomiting, and ataxia. These events are also commonly associated with phenytoin IV therapy.

Similar adverse events were noted following both fosphenytoin IV and IM administration. These were nystagmus, ataxia, nervousness, somnolence, fever, and vomiting. Nystagmus, ataxia, and vomiting were the most commonly reported AEs with both routes of administration. Nystagmus and ataxia were more commonly reported following IM administration and vomiting was more commonly reported following IV administration. The percent of subjects for whom nervousness, somnolence, and fever were reported was similar for IV and IM administration (ie, approximately 6% to 8%). Hypotension, pruritus, and rash were reported in approximately 5% to 6% of subjects after IV administration but not after IM administration.

Adverse events reported in subjects who received doses greater than 20 mg/kg and/or at infusion rates greater than 3 mg/kg/min (n = 23) were similar in type and intensity to those reported for all pediatric subjects. Vomiting (6/23, 26%) and nystagmus (5/23, 22%) were most commonly reported in subjects who received high doses and/or rapid infusion rates.

Table 6 Adverse Events Reported in > 2% of Subjects in Study 982-028 (All and Treatment-Related) by Decreasing Frequency

Table 13. Adverse Events Reported in ≥2% of the Total Number of Subjects in Study 982-028 (All and Treatment-Related) by Decreasing Frequency

Body System Preferred Term	Neonates N = 21		Infants N = 33		Children N = 45		Adolescents N = 14		Total N = 113	
	All AEs n (%)	Treatment-Related AEs n (%)	All AEs n (%)	Treatment -Related AEs n (%)	All AEs n (%)	Treatment -Related AEs n (%)	All AEs n (%)	Treatment -Related AEs n (%)	All AEs n (%)	Treatment -Related AEs n (%)
All Body Systems	11 (52.4)	4 (19.0)	23 (69.7)	14 (42.4)	27 (60.0)	18 (40.0)	11 (78.6)	9 (64.3)	72 (63.7)	45 (39.8)
(Central) Nervous	2 (9.5)	0 (0.0)	13 (39.4)	8 (24.2)	20 (44.4)	14 (31.1)	7 (50.0)	6 (42.9)	42 (37.2)	28 (24.8)
Nystagmus	0 (0.0)	0 (0.0)	6 (18.2)	5 (15.2)	11 (24.4)	10 (22.2)	5 (35.7)	5 (35.7)	22 (19.5)	20 (17.7)
Ataxia	0 (0.0)	0 (0.0)	4 (12.1)	4 (12.1)	9 (20.0)	8 (17.8)	2 (14.3)	2 (14.3)	15 (13.3)	14 (12.4)
Somnolence	0 (0.0)	0 (0.0)	3 (9.1)	1 (3.0)	3 (6.7)	2 (4.4)	2 (14.3)	2 (14.3)	8 (7.1)	5 (4.4)
Nervousness	1 (4.8)	0 (0.0)	4 (12.1)	1 (3.0)	1 (2.2)	0 (0.0)	1 (7.1)	0 (0.0)	7 (6.2)	1 (0.9)
Agitation	1 (4.8)	0 (0.0)	1 (3.0)	1 (3.0)	1 (2.2)	1 (2.2)	0 (0.0)	0 (0.0)	3 (2.7)	2 (1.8)
Body as a Whole	5 (23.8)	3 (14.3)	6 (18.2)	2 (6.1)	10 (22.2)	3 (6.7)	7 (50.0)	4 (28.6)	28 (24.8)	12 (10.6)
Fever	0 (0.0)	0 (0.0)	4 (12.1)	0 (0.0)	5 (11.1)	1 (2.2)	0 (0.0)	0 (0.0)	9 (8.0)	1 (0.9)
Injection site pain	0 (0.0)	0 (0.0)	1 (3.0)	1 (3.0)	1 (2.2)	1 (2.2)	3 (21.4)	3 (21.4)	5 (4.4)	5 (4.4)
Injection site reaction	3 (14.3)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	4 (3.5)	1 (0.9)
Injection site edema	0 (0.0)	0 (0.0)	2 (6.1)	2 (6.3)	1 (2.2)	1 (2.2)	1 (7.1)	1 (7.1)	4 (3.5)	4 (3.5)
Face edema	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	2 (4.4)	0 (0.0)	1 (7.1)	0 (0.0)	4 (3.5)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	2 (4.4)	0 (0.0)	1 (7.1)	0 (0.0)	4 (3.5)	0 (0.0)
Injection site inflammation	0 (0.0)	0 (0.0)	1 (3.0)	1 (3.0)	1 (2.2)	1 (2.2)	1 (7.1)	1 (7.1)	3 (2.7)	3 (2.7)
Digestive	2 (9.5)	0 (0.0)	10 (30.3)	3 (9.1)	9 (20.0)	3 (6.7)	4 (28.6)	2 (14.3)	25 (22.1)	8 (7.1)
Vomiting	2 (9.5)	0 (0.0)	9 (27.3)	3 (9.1)	8 (17.8)	3 (6.7)	2 (14.3)	1 (7.1)	21 (18.6)	7 (6.2)
Cardiovascular	2 (9.5)	1 (4.8)	6 (18.2)	4 (12.1)	4 (8.9)	1 (2.2)	2 (14.3)	1 (7.1)	14 (12.4)	7 (6.2)
Hypotension	1 (4.8)	1 (4.8)	1 (3.0)	1 (3.0)	3 (6.7)	1 (2.2)	0 (0.0)	0 (0.0)	5 (4.4)	3 (2.7)
Bradycardia	0 (0.0)	0 (0.0)	3 (9.1)	2 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	2 (1.8)
Skin and Appendages	0 (0.0)	0 (0.0)	3 (9.1)	0 (0.0)	7 (15.6)	5 (11.1)	1 (7.1)	0 (0.0)	11 (9.7)	5 (4.4)
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (13.3)	4 (8.9)	0 (0.0)	0 (0.0)	6 (5.3)	4 (3.5)
Rash	0 (0.0)	0 (0.0)	2 (6.1)	0 (0.0)	2 (4.4)	2 (4.4)	1 (7.1)	0 (0.0)	5 (4.4)	2 (1.8)
Special Senses	1 (4.8)	0 (0.0)	1 (3.0)	0 (0.0)	4 (8.9)	2 (4.4)	1 (7.1)	0 (0.0)	7 (6.2)	2 (1.8)
Eye disorder	1 (4.8)	0 (0.0)	1 (3.0)	0 (0.0)	1 (2.2)	1 (2.2)	0 (0.0)	0 (0.0)	3 (2.7)	1 (0.9)

Abbreviations: AE = adverse event; n = number of evaluable subjects experiencing each AE; N = total number of subjects
Source: CSR 982-028, Appendix B.13

7.3.5 Submission Specific Primary Safety Concerns

Cardiovascular Adverse Events Related to High Unbound Phenytoin Levels Following a Loading Dose

A primary safety concern is the possible occurrence of significant cardiovascular adverse effects (hypotension and/or cardiac arrhythmia) in the setting of high unbound phenytoin levels following a loading dose.

The possibility of a relationship between high phenytoin concentrations and cardiovascular adverse events, particularly hypotension and bradycardia was an issue of concern in the pediatric development program. Reaching adequate peak plasma concentrations of free phenytoin in a rapid manner is important for treatment of status epilepticus. It is also essential that peak plasma levels be safe in patients. Therefore, a loading dose should rapidly deliver adequate levels of free phenytoin while avoiding high levels to minimize adverse drug reactions.

The lower and upper thresholds of peak plasma concentrations (Cmax) of phenytoin with respect to cardiovascular adverse effects are not well-defined. Therefore, as discussed in section 6.1.1 of this review, the sponsor chose 0.950 to 7.47 µg/mL as a reference range for Cmax. Accordingly, any concentration that fell above 7.47 µg/mL was considered as a high concentration.

The Table 6 (sponsor's Table 11 from Clinical Overview) presents subjects in Study 982-028 who had unbound plasma phenytoin concentrations of 7.47 ug/mL or higher at any time after the loading dose and adverse events reported for each of those subjects. Seven subjects in this study had high phenytoin levels (as defined in section 6 of this review) after the loading dose.

Among these 7 subjects, 1 experienced a severe cardiovascular adverse event (death). This subject (Site 004, Subject 007) died of cardiac arrest and is discussed in section 7.3.1 of this review. This subject received a fosphenytoin loading dose of 24.4 mg PE/kg and had an unbound phenytoin level of 14.4 ug/mL. Notably, the percentage of total unbound phenytoin was high at 51.5%.

None of the other 6 subjects who had high unbound phenytoin levels had cardiovascular adverse events. Of note, 1 subject (Site 011, Subject 006) had an unbound phenytoin level of 14.2 ug/mL but did not experience an adverse event, suggesting that high levels of phenytoin may not always be directly associated with cardiovascular adverse events.

Cardiovascular adverse events were reported for 14 subjects in Study 982-028 and included hypotension (5), bradycardia (3), vasodilatation (2), heart arrest (1), heart block (1), cardiovascular disorder (1), tachycardia (1), and arrhythmia (1). Pharmacokinetics data, available for 9 of the 14 subjects, revealed that only 1 of the subjects with cardiovascular adverse events had elevated plasma phenytoin levels; this was the premature neonate who died (Site 004, Subject 007) after suffering multiple neonatal medical problems as previously described in this review.

The possible correlation between high unbound fosphenytoin levels and the adverse events in these subjects is further discussed below.

Table 7 Listing of Subjects With Unbound Phenytoin Concentrations Greater Than 7.47 µg/mL and Associated Adverse Events (Study 982-028)

Age Group (Site No./ Subject No.)	Dose (mg/ kg)	PK Time (min)	Total PHT	Free PHT	% PHTFF	AE	Intensity	Drug related?	Out-come
Neonate (4/7)	24.4	3.417	27.9	14.4	51.5	Heart arrest	Severe	Unrelated	Death
Infant (7/4)	17.9	6.833	37.6	8.44	22.4	Rash	Moderate	Unrelated	RCD
						Constipation	Mild	Unlikely	RCD
						Vomiting	Mild	Unlikely	RCD
Infant (7/16)	18	6.967	36.1	8.09	22.4	Nystagmus	Mild	Probably	RCD
		16.000	25.9	11.1	42.9	Vomiting	Mild	Probably	RCD
						Nystagmus	Mild	Probably	RCD
Infant (21/2)	15	40.733	50.3	9.22	18.4	Nervousness	Mild	Unlikely	RCD
		70.800	47.6	8.31	17.5	Vomiting	Mild	Unlikely	RCD
						Eye Disorder	Mild	Unlikely	NYR
						Reflexes Inc	Mild	Unlikely	NYR
Children (3/4)	20	12.567	33.9	7.78	22.9	Cough Inc	Mild	Probably	RCD
						Agitation	Mild	Probably	RCD
						Confusion	Mild	Probably	RCD
						Vomiting	Mild	Probably	RCD
						Ataxia	Mild	Possibly	UNK
						Nystagmus	Mild	Unrelated	UNK
Children (11/6)	20	7.250	60.6	14.2	23.4	No AE reported	NA	NA	NA
Adolescent (17/10)	20	7.333	35	11.2	31.9	Myasthenia	Moderate	Unrelated	NYR
						Pain	Moderate	Unrelated	NYR
						Vomiting	Mild	Unrelated	RCD
						Face edema	Moderate	Unrelated	NYR

Note: Outcome of recovered includes event resolved. Subject 009 from Center 005 had high unbound phenytoin concentrations but did not experience an AE; therefore, is not included in this table.
Abbreviations: AE = adverse event, Inc = increased; NA = not applicable, NYR = not yet recovered, PHT = phenytoin, PHTFF = phenytoin/free fosphenytoin, PK = pharmacokinetics. RCD= recovered, UNK = unknown
Source: CSR 982-028, Appendices B.19, C (Table 3.1), and D.4

Subjects With High Unbound Phenytoin Levels

To further investigate any potential relationship between elevated phenytoin levels and adverse events, the clinical course and the adverse events for the 8 subjects with high unbound phenytoin concentrations (upper 90% bound and greater than or equal to 7.47 µg/mL) in Study 982-028 were examined following fosphenytoin IV loading and/or maintenance doses. These 8 subjects are the previously mentioned 7 subjects with high levels and AEs plus one subject with high levels and no AEs.

Narrative summaries are presented below:

Study 982-028, Center 004, Subject Number 007: This 11-day-old (premature neonate) female with neonatal SE was hospitalized for Escherichia coli sepsis and meningitis and subsequently died due to cardiac arrest on Study Day 1. The subject had a history of patent ductus arteriosus, intraventricular hemorrhage, and thrombocytopenia due to disseminated intravascular coagulation disorder, hypotension, bradycardia, respiratory distress syndrome with interstitial emphysema. The subject received a loading dose of 22.00 mg (24.44 mg PE/kg) fosphenytoin IV, which was infused at a rate of 1.63 mg/kg/min for continuing seizures. The unbound phenytoin level measured 3.42 minutes after the IV loading dose was administered on Study Day 1 was reported as 14.4 µg/mL. Concomitant medications included dopamine, dobutamine, phenobarbital, lorazepam, fentanyl, cefotaxime, tobramycin, clindamycin, and vancomycin. Prior to the infusion of the study medication, the subject was hemodynamically unstable, with a blood pressure of 31/19 mm Hg and a heart rate of 147 beats per minute (bpm), and was receiving maximum medical support. During the infusion of study medication, the subject's hemodynamic status continued to decline. Approximately 10 minutes after the infusion was complete, the subject went into cardiopulmonary arrest and died. The investigator considered this event definitely unrelated to fosphenytoin.

Reviewer Note:

See under narrative for this patient in section 7.3.1 of this review.

Study 982-028, Center 005, Subject Number 009: This 1-day-old (premature neonate) white female entered the study with a history of possible sepsis and hypotension, and was suffering from respiratory distress syndrome, insulin-dependent diabetes mellitus, acute perinatal anemia, oliguria, patient ductus arteriosus, and hypoxic ischemic encephalopathy. The subject received an IV loading dose of 50.0 mg (15.63 mg/kg) fosphenytoin infused at a rate of 3.021 mg/kg/min for seizures. The subject received two IV maintenance administrations of 2.56 mg/kg fosphenytoin on Study Days 2 and 3, and one IV maintenance administration of 2.56 mg/kg fosphenytoin on Study Day 4. Phenytoin concentration measured 38.3 µg/mL at 05:30 AM on Study Day 5 (21 hours after the end of the most recent maintenance dose) and 1 additional fosphenytoin maintenance dose (2.56 mg/kg) was given before the elevated phenytoin concentration was known. Phenytoin concentration increased to 48.2 µg/mL, fosphenytoin was discontinued, and the subject was withdrawn from the study on Study Day 5. Concomitant medications included acyclovir, caffeine, furosemide, phenobarbital, dopamine, and heparin. No AEs occurred in conjunction with the elevated unbound phenytoin levels. The subject recovered by study closeout. The adverse event of elevated unbound phenytoin was considered nonserious, mild in intensity, and related to study drug.

Reviewer Note:

This premature neonate received a loading dose of 15 mgPE/kg but then was given additional fosphenytoin "maintenance administrations" with the result of her receiving a total of 25.87 mgPE/kg before a level of phenytoin was reported. This neonate was also on phenobarbital which could have raised the phenytoin level. Although she had an extremely high unbound level of 48.2 ug/ml, she apparently did not have any adverse effects attributable to this level.

Study 982-028, Center 007, Subject Number 004: On Study Day 1, a 1-year- old White female infant received a loading dose of 140 mg (17.9 mg/kg) fosphenytoin IV, which was infused at a rate of 2.46 mg/kg/min. Her unbound phenytoin level, measured 6.83 minutes after the IV loading dose was 8.44 µg/mL. Medical history included infection and seizure disorder. Concomitant medications included Pepcid, ceftriaxone, phenytoin, Kefzol, and phenobarbital. Adverse events included rash, which was considered not serious, moderate in intensity, and definitely unrelated to study drug. The subject also experienced adverse events of constipation and vomiting, which were considered nonserious, mild in intensity, and unlikely related to study drug.

Reviewer Note:

This one year old infant was already receiving phenytoin (no level prior to the loading dose is given) and on phenobarbital. The level attained after loading is only slightly above the sponsor's "reference range for Cmax) which, as discussed above, is not based on the occurrence of adverse events.

Study 982-028, Center 007, Subject Number 016: On Study Day 1, this 1-year- old female infant received a loading dose of 180 mg (18.0 mg/kg) fosphenytoin IV, which was infused at a rate of 3.0 mg/kg/min. Her unbound phenytoin levels, approximately 7 and 16 minutes after infusion, were 8.09 µg/mL and 11.1 µg/mL, respectively. Medical history included otitis media, infection, lethargy, and respiratory depression. Concomitant medications included amoxicillin (administered 06 July 1997, prior to the study, which began on 07 July 1997 and per protocol was listed as a concomitant medication), Ativan, phenobarbital, ceftriaxone, acyclovir, Pepcid, Septra, Tegretol, and Versed. Additional concomitant medications included Decadron, Tylenol, calcium chloride, and magnesium sulfate. This subject experienced the adverse events of nystagmus and vomiting, which were mild in severity, considered nonserious, and unlikely to be related to the study drug.

Reviewer Note:

The loading dose of 18 mgPE/ml is in the range (15-20 mgPE/kg) this reviewer is recommending for loading dose for status epilepticus. The level obtained is not much above the sponsor's "reference range". There is a long list of concomitant medications, several of which could have contributed to the observed nystagmus and vomiting. Even if these adverse effects are attributed to fosphenytoin, they would be acceptable in the context of treating status epilepticus.

Study 982-028, Center 021, Subject Number 002: On Study Day 1, this 232-day-old Black male infant received a loading dose of 105 mg (15.0 mg/kg) fosphenytoin IV, which was infused at a rate of 1.50 mg/kg/min. His unbound phenytoin levels, 41 and 71 minutes after infusion, were 9.22 µg/mL and 8.31 µg/mL, respectively. Medical history included cystic fibrosis, right parietal hemorrhage, hydrocephaly, pleural effusion, pneumothorax with respiratory distress, and craniotomy. Concomitant medications included Pancrease, chloral hydrate, Albuterol, lidocaine, thrombin, fentanyl, phenytoin, Versed, Calciferol, Ergocalciferol, mannitol, and cefamandole. Additional concomitant medications included heparin, Dulcolax, potassium chloride, morphine sulfate, bacitracin ointment, acetaminophen, rocuronium, Zantac, vitamin A, vitamin D, vitamin E, vitamin K, calcium chloride, Lasix, propofol, Mivacron, atropine, pentobarbital, and simethicone. Thrombin and lidocaine were both administered 08 July 1997, 3 days prior to the study, which began 11 July 1997, and so are listed per protocol as concomitant medications. This subject experienced adverse events of nervousness, vomiting, eye disorder, and reflexes increased, all of which were considered nonserious, mild in intensity, and unlikely related to the study drug. All adverse events resolved, with the exception of eye disorder and reflexes increased,which had not yet resolved.

Reviewer Note:

Although this is not explicitly stated, it would appear that this patient was on phenytoin prior to a craniotomy and subsequently was nonurgently loaded with a loading dose of 15 mgPE/kg. The levels attained were slightly above the sponsor's "reference range", but there were no cardiovascular adverse effects.

Study 982-028, Center 003, Subject Number 004: On Study Day 1, this 10-year-old Black male child received a loading dose of 540 mg (20.0 mg/kg) fosphenytoin IV, which was infused at a rate of 2.0 mg/kg/min. His unbound phenytoin level, 13 minutes after infusion, was 7.78 µg/mL. Medical history included anaplastic astrocytoma, hypothyroidism, anemia, seizure disorder, chronic constipation, anorexia, and tumor resection. Concomitant medications included Synthroid, Pericolace, Tegretol, and aspirin. This subject experienced the adverse events of increased cough, agitation, increased confusion, vomiting, ataxia, and horizontal nystagmus, all of which were

considered nonserious, mild in severity, and probably related to the study drug. The subject recovered from all adverse events with the exception of nystagmus and ataxia, for which the clinical outcomes were unknown.

Reviewer's Note:

The indication for the fosphenytoin (possibly commencement of phenytoin therapy after neurosurgery for a brain tumor) is not stated. The loading dose is at the upper end of the range of dosing this reviewer is recommending for status epilepticus. The adverse effects were central nervous system rather than cardiovascular effects and might be attributable in part to the brain tumor or its resection.

Study 982-028, Center 011, Subject Number 006: On Study Day 1, this 9-year-old male child received a loading dose of 400 mg (20.0 mg/kg) fosphenytoin IV, which was infused at a rate of 3.0 mg/kg/min. His unbound phenytoin level, 7 minutes after infusion, was 14.2 µg/mL. Medical history included Angelman Syndrome, seizure disorder, otitis media, asthma, and autistic-like behavior. Concomitant medications included phenobarbital, lamotrigine, and phenytoin. No adverse events were reported for this subject.

Reviewer Note:

The loading dose is at the upper end of the range of dosing this reviewer is recommending for status epilepticus. No adverse effects were reported.

Study 982-028, Center 017, Subject Number 010: On Study Day 1, this 13-year-old white female adolescent received a loading dose of 950 mg (20.0 mg/kg) fosphenytoin IV, which was infused at a rate of 3.0 mg/kg/min. Her unbound phenytoin level, 7 minutes after the IV loading dose, was 11.2 µg/mL. Medical history included right-sided motor seizures, left frontal parietal temporal craniotomy, brain tumor removal, tonsils and adenoids removal. Concomitant medications included Versed, amoxicillin, Decadron, Zantac, Tylenol, Tylenol with codeine, Toradol, Zofran, Tegretol, and Depakote. This subject experienced the adverse events of myasthenia, pain, vomiting, and face edema, which were all considered nonserious and definitely not related to the study medication. Myasthenia, pain, and face edema were considered moderate in intensity and the clinical outcome of the events was reported as not resolved at the time of the report. Vomiting was considered mild in intensity and the clinical outcome for this event was reported as resolved.

Reviewer Note:

The loading dose is at the upper end of the range of dosing this reviewer is recommending for status epilepticus. The phenytoin level attained was within the range predicted by modeling for this fosphenytoin dose. It appears that the patient had a craniotomy for a brain tumor resection and was loaded with fosphenytoin to replace oral Depakote and Tegretol which did not have intravenous formulations at that time. The adverse effect of vomiting ("considered mild") is the only one that seems likely to be attributable to fosphenytoin.

Reviewer Note on All Eight Narratives:

Considering all these cases, there are relatively few cases (eight) of elevated fosphenytoin levels; these are distributed across the pediatric age range (2 neonates, 3 infants, 2 children and 1 adolescent). With the exception of the one fatality (Center 004 Number 007, a neonate who was desperately ill and hemodynamically unstable before the fosphenytoin infusion), there appear to have been no significant cardiovascular adverse effects associated with the observed high phenytoin levels. One of the neonates (Center 005, Number 009) , had an observed level that well exceeded by a factor of 3 the predicted values (by modelling) from the dose this reviewer is recommending for status epilepticus without observed cardiovascular adverse effects.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

See section 7.3.4

7.4.2 Laboratory Findings

In Study 982-028, laboratory data obtained during the studies were collected at screening, during treatment, and at follow-up. A review of available clinical laboratory data did not identify any notable changes or trends in clinical laboratory values. No consistent changes were noted within or across age groups

7.4.3 Vital Signs

In Study 982-028, blood pressure and heart rate were monitored at screening, during and after treatment, and at follow-up visits. Modest reductions in mean blood pressure and minor changes in mean respiratory rate were observed across all age groups with both IV and IM administration.

7.4.4 Electrocardiograms (ECGs)

In Study 982-028, cardiac rhythm was monitored by ECG at each infusion and did not reveal any clinically significant effect of fosphenytoin on cardiac rhythm. A few subjects experienced mild changes in heart rate.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

Not applicable.

7.5.1 Dose Dependency for Adverse Events

See 7.3.5

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

See current labeling.

7.5.4 Drug-Disease Interactions

See current labeling.

7.5.5 Drug-Drug Interactions

See current labeling.

7.6 Additional Safety Evaluations

Age Groups within the Pediatric Population

Eleven premature newborns received fosphenytoin throughout the course of the pediatric development program. Of these, 6 subjects experienced 12 adverse events. The types of adverse events experienced by these premature newborns (agitation, alkalosis, drug [phenytoin] level increased, dyspnea, edema, heart arrest, hematuria, hyperglycemia, hypotension, injection-site reaction, and nervousness) were generally similar to those experienced by older pediatric subjects. Hematuria (reported in 2 subjects; see Section 2.5.6.7.1 for more detail) was the only event occurring in more than a single subject. One SAE (heart arrest) was reported, but was not considered related to study medication.

Three of the 12 adverse events were considered drug-related (drug [phenytoin] level increased, hypotension, injection-site reaction); however, all were nonserious and all events resolved by the end of the study period.

The highest frequency of drug-related adverse events was reported for the adolescent age group, whereas, the lowest frequency was reported for neonates. The incidence of drug-related adverse events was similar in infants and children. Most adverse events (any age group) were mild-to-moderate in severity. Severe adverse events were reported only in the neonatal population and were reported in 3 premature newborns.

7.7 Additional Submissions / Safety Issues/ Summary of Safety

Since there were no randomized, double-blind controlled trials to support this pediatric labeling supplement, the safety data has been assembled from the pediatric studies of PK, safety and tolerability; from the published literature, and from postmarketing reports. In section 8 of this review, the postmarketing reports are discussed in the context of a scrutiny of pediatric adverse events of special interest which combined data from the pediatric studies and from postmarketing reports.

The pediatric safety data from all sources can be summarized as follows:

Safety data from the pediatric clinical studies indicate that fosphenytoin is generally safe and well-tolerated in pediatric patients from birth through 16 years of age, supporting the use of fosphenytoin in this age group.

A cumulative review of the relevant published literature did not provide significant new safety information for fosphenytoin and was consistent with the known safety profile of the drug.

Pediatric postmarketing reports of reports of hematuria, cardiovascular events, hypotension, hyperglycemia, pruritus, agitation and nervousness, vomiting, purple glove syndrome, infusion site reactions, rash and serious dermatologic reactions, medication error and overdoses, fatal reports, other serious adverse events, and non-serious reports did not identify any new safety signals.

Medication errors including overdoses have occurred with fosphenytoin use, and the Sponsor has implemented numerous mitigations to reduce the risk of medication errors. In the US, where changes have been made to the product and vial labeling, the rate of medication errors has been low.

A comparison of pediatric and adult postmarketing adverse event ratios did not identify any new safety signals in the pediatric patient population compared to adults.

Reviewer Note:

The overall safety profile of fosphenytoin in the pediatric clinical studies supports its use for the same indications that are currently labelled for adults.

8 Postmarket Experience

In the Division's advice letter (December 2015), the Division asked the sponsor to provide a Safety Update for fosphenytoin use in the pediatric patient population. This update includes information from the sponsor's global safety database including postmarketing data, clinical study information, and pertinent information from the published literature. Requested adverse events of special interest for discussion include:

- Anticonvulsant Serum Plasma Levels
- Hypotension

- Cardiovascular events
- Hyperglycemia
- Pruritus
- Agitation and Nervousness
- Rash and Serious Dermatologic Reactions
- Vomiting
- Hematuria
- Purple glove Syndrome
- Infusion site Reactions
- Medication Errors and Overdose
- Fatality reports
- Postmarketing Reports of Other Serious Adverse Events New safety signals???
- Postmarketing Events of Non-serious Cases
- Pediatric and Adult Safety Profile Analysis

Each of these topics are addressed as follows based on safety data from both the previously discussed clinical studies and from post-marketing reports.

Anticonvulsant Serum Plasma Levels

In pediatric clinical studies, free phenytoin levels greater than 7.47 µg / mL were reported for 7 subjects in study 982-028. The most common adverse events among these subjects were as follows: vomiting (5 subjects) and nystagmus (2 subjects).

In postmarketing pediatric reports, increases and decreases in serum phenytoin levels have been reported. The most frequently reported events in the 14 cases involving increased serum phenytoin levels were: Accidental overdose (4); Cardiac arrest (3); Bradycardia, Convulsion, Hypotension, Hypoxia, and Tachycardia (2 each). In the 13

cases involving decreased serum phenytoin levels, the most frequently reported events were: Drug ineffective (4), Drug interaction (4), and Convulsion (3).

In the majority of reports, a reason for the increase or decrease in serum phenytoin levels could not be determined based on the available information. In a few of the reports involving elevated phenytoin level, concomitant medications known to interact and increase serum phenytoin levels, and laboratory testing 2 hours following fosphenytoin administration may have contributed to the finding of increased phenytoin levels. In 7 of the 13 cases reporting decreased serum phenytoin levels, concomitant medications known to interact with and reduce serum phenytoin levels may have contributed to decreased phenytoin levels.

Based upon the review of the clinical study data, published literature, and postmarketing reports of increased and decreased serum phenytoin levels, no new safety signals were identified in the pediatric population.

Hypotension

In clinical studies, there were 5 non-serious reports of hypotension in pediatric patients, all in study 982-028. Hypotension occurred across most age groups, was generally mild, required no intervention, and resolved before study end.

Hypotension has been reported in children treated with fosphenytoin in both the literature and postmarketing reports. In most cases, hypotension has occurred in the setting of severe underlying illness, co-suspect and/or multiple concomitant medications, or overdose. As such, it is often difficult to assess the relative contribution of fosphenytoin to the hypotension reported in these cases. Nonetheless, a potential contribution of fosphenytoin cannot be ruled out. Hypotension is listed in the Warnings and Adverse Reactions sections of the fosphenytoin labeling. Based upon the review of the clinical study data, published literature and postmarketing reports of hypotension, no new safety signals were identified in the pediatric population.

Cardiovascular events

During the pediatric clinical development program, fifteen subjects experienced cardiovascular adverse events (14 subjects from the 982-028 study and 1 subject from the 982-015 study). There were 14 non-serious cardiovascular events, of which the majority were considered unrelated to study treatment.

Cardiovascular events including hypotension, bradycardia and asystole have been reported in the setting of fosphenytoin overdose in both the literature and postmarketing reports. Three (25%) of the 12 literature reports discussed involved overdoses. Twelve (44%) of the 27 postmarketing cases reported an overdose and 1 case involving medication error reported a dose that was 6 times the maximum recommended dosage.

In the majority of cases, the relationship between the reported cardiovascular events and the administration of fosphenytoin is often complicated by the underlying medical conditions (including seizures and status epilepticus, head injury, and sepsis) as well as cosuspect and/or concomitant medications. Nonetheless, the timing of some of the events in relationship to fosphenytoin administration suggests a possible causal role.

Based on the review of the clinical study data, published literature and postmarketing reports, no new cardiovascular safety signal was identified in the pediatric population.

The previously identified cardiovascular risks are prominently discussed in the currently approved and proposed fosphenytoin labeling including a box warning about maximum doses and rate of administration.

Hyperglycemia

One subject (a premature neonate in study 982-028) experienced hyperglycemia which was considered unrelated to study treatment. Confounding factors including concomitant drugs and overdoses were identified in the published literature reports. The majority of postmarketing reports occurred in the setting of fosphenytoin overdose. A contributory role could not be excluded in all postmarketing reports.

The Precautions section of the fosphenytoin labeling states: “Hyperglycemia, resulting from phenytoin’s inhibitory effect on insulin release, has been reported. Phenytoin may also raise the serum glucose concentrations in diabetic patients.”

Based upon the review of the clinical study data, published literature and postmarketing reports of hyperglycemia, no new safety signal was identified in the pediatric population.

Pruritus

Pruritus has been reported as mild to moderate reactions in the pediatric development Program (6 subjects in the 982-028 study and 2 subjects in the 982-016 study). Pruritus has been reported in both the literature and postmarketing reports. One of the postmarketing reports occurred in the context of accidental overdose. Pruritus is listed in the Adverse Reactions section of the fosphenytoin labeling. Based on the review of the clinical trial data, published literature and postmarketing reports of pruritus, no new safety signal was identified in the pediatric population.

Agitation and Nervousness

In the pediatric development program, 4 subjects experienced agitation and 7 subjects experienced nervousness. These events were mild or moderate in intensity; none of the

events were considered serious and most had significant confounding factors. Review of the literature identified 3 reports of agitation, all of which had significant confounders.

The safety database identified 1 report of agitation associated with visual hallucinations. Agitation and Nervousness are listed in the Adverse Reactions section of the fosphenytoin labeling. Based upon the review of the clinical study data, published literature and postmarketing reports of agitation and nervousness, no new safety signal was identified in the pediatric population.

Rash and Serious Dermatologic Reactions

Rash has been reported as mild to moderate reactions in the pediatric development program. There were no reports of serious dermatologic reactions in the pediatric development program. Rash and serious dermatologic reactions have been reported in the setting of fosphenytoin use in both the literature and postmarketing reports. Of the 13 postmarketing reports, 5 cases reported co-suspect medications and 7 of the 13 cases reported concomitant medication use; however, in each of the reports involving rash, urticaria and serious dermatologic reactions an association between the reported event and fosphenytoin could not be excluded.

Rash, DRESS/Multiorgan hypersensitivity, and serious dermatologic reactions including Stevens-Johnson syndrome and Toxic epidermal necrolysis (TEN) have been reported in patients receiving anticonvulsants including fosphenytoin and phenytoin. Rash and urticarial are listed in the Adverse Reactions section of the fosphenytoin labeling.

Vomiting

In clinical trials, vomiting was a common adverse event in pediatric patients and was reported to be mild in severity. In Study 982-028, the incidence of vomiting was increased in subjects with elevated (> 7.47 µ/ per mL) free phenytoin levels and appeared more frequently in subjects receiving intravenous administration than subjects receiving intramuscular administration. In the majority of literature and postmarketing reports, vomiting was reported in an age group $\leq$ 9 years of age; however, given the small number of cases reported it is difficult to make conclusions regarding the incidence of vomiting in younger (compared to older) pediatric populations. Two of the 4 postmarketing reports were associated with overdose; and 1 case reported elevated serum phenytoin levels.

Vomiting is listed in the Adverse Reactions and Overdosage sections of the fosphenytoin labeling. Based upon the review of the clinical study data, published literature and postmarketing reports of vomiting, no new safety signal was identified in the pediatric population.

Hematuria

There was 1 report of mild hematuria and 1 report of moderate hematuria in clinical studies. Literature review revealed 1 report of hematuria in a pediatric patient in status epilepticus on multiple medications occurring in the setting of rewarming following medically induced hypothermia. No reports of hematuria involving pediatric patients were identified in the safety database. Based on this review, no new safety signals were identified

Purple Glove Syndrome

No reports of Purple Glove Syndrome were identified in the pediatric clinical studies, literature, and postmarketing safety reviews. There were 3 cases reporting non-serious events extravasation coded to the PT Oedema and 1 non-serious report of phlebitis identified in the safety database.

The currently approved and proposed Warnings and Precautions section of the fosphenytoin labeling discusses “Local toxicity (Purple Glove Syndrome)”. Based on review of the clinical study data, published literature and postmarketing data, no new safety signal was identified in the pediatric population.

Infusion Site Reactions

In clinical studies, infusion site reactions were common adverse events in the pediatric studies. There was 1 report of a severe infusion site reaction (erythema). All infusion site reactions in clinical study subjects were self-limiting and all reactions resolved without complications.

There were no reports of infusion site reactions involving the pediatric population in the literature. The majority of postmarketing reports provided limited information regarding infusion site reactions. Injection site reactions are listed in the Adverse Reactions section of the fosphenytoin labeling. Based on review of the clinical study data, published literature and postmarketing reports of infusion site reactions, no new safety signal was identified in the pediatric population.

Medication Errors and Overdose

Review of the clinical study data did not identify any reports of medication errors or overdoses occurring in the pediatric patient population. There was 1 report of medication error in the published pediatric literature suggesting cardiomyopathy resulting from administration of an incorrect dose of fosphenytoin sodium. Forty-two cases were identified in the postmarketing dataset. Three of the 42 cases involved overdoses with drugs other than fosphenytoin. In the remaining 39 cases, 3 cases

involved non-overdose medications errors, 1 case involved an underdose and 35 cases involved reported overdoses.

Fatality Reports

There were 2 non-drug-related deaths reported in the clinical studies which are discussed in detail in section 7.3.1 of this review.

Nineteen of the 23 postmarketing cases reporting fatal outcomes also involved patients with severe underlying conditions including: convulsion or seizures (4 patients); coma, encephalitis, histiocytosis, haematophagic, mechanical ventilation, Escherichia infection, Staphylococcal pneumonia, and epilepsy (1 case); convulsion following a fall (1 case), convulsions following head trauma (1 case), convulsion, probable viral myocarditis and an apical mural thrombosis (1 case), convulsion, head injury due to fall [fracture of the right temporal bone with an associated small subdural hematoma] (1 case), seizure and Down syndrome (1 case), status epilepticus and hypotonia (1 case), numerous hospitalizations and difficult amenable epilepsy (1 case); Pertussis, possible secondary bacterial pneumonia, possible sepsis, encephalitis, status epilepticus (1 case), severe convulsions (1 case), status epilepticus (3 case), status epilepticus and prior cardiac surgery for transposition of great vessels (1 case), and status epilepticus, leucodystrophy, colonic ischemia with enterocolitis complicated by a blocked perforation, peritoneal mass, proctorrhagia (1 case). Three cases reported an underlying history of ill-defined disorder and 1 case involved a newborn who experienced fetal exposure to fosphenytoin in-utero and died from an unknown cause following delivery.

Of the 23 postmarketing cases reporting fatal outcomes, 3 deaths were attributed to underlying illness (intestinal ischemia; refractory status epilepticus; septic shock and multiorgan failure); 12 deaths were associated with fosphenytoin overdoses and/or medication errors; 6 deaths were associated with cardiac events; 1 death was associated with a hypersensitivity reaction; and 1 case involved a newborn who died from an unknown cause following delivery.

The risk of death is appropriately addressed in the boxed warning, Warnings and Precautions, and Overdosage sections of currently approved and proposed labeling.

On the basis of this review, no new safety signal was identified for the pediatric population.

Postmarketing Reports of Other Serious Adverse Events: No New Safety Signals

Of the 141 fosphenytoin pediatric reports, there were 25 serious cases which were not previously discussed in the above safety topics.

Review of the 25 other serious adverse event cases, as discussed in Table 8 (Table 17 from the sponsor's Safety Update), did not identify any new safety signals.

Table 8 Summary of PTs for Other Serious Fosphenytoin Pediatric Reports (n=25)

SOC	PT Count	Comment
Blood and lymphatic system disorders	8	The events include: Anemia (1), Leukopenia (2), Neutropenia (2), and Thrombocytopenia (3). Review of these cases did not identify any new safety signals.
General disorders and administration site conditions	11	These events include: Crying (1), Drug ineffective (6), Drug ineffective for an unapproved indication (1), Drug interaction (2), and Feeling abnormal (1). The 6 cases of drug ineffective reported Phenobarbital as a co-suspect drug. No new safety signals were identified.
Hepatobiliary disorders	2	The first event was Hepatitis in a 6-year-old male. The patient was receiving multiple medications. Limited clinical details were provided. In the second case a 16-year-old female experienced acute cytolytic hepatitis after receiving a single dose of fosphenytoin and clonazepam. Fosphenytoin was discontinued the same day and hepatitis improved. At the time of reporting, the patient had not recovered. No new safety signal was identified.
Investigations	8	The events include: Amylase increased (1), Blood calcium decreased (1), Blood creatine phosphokinase increased (2), Calcium ionized decreased (1), Drug screen false positive (1), Haemoglobin decreased (1), Lipase increased (1). Review of these cases did not identify any new safety signals.
Metabolisms and nutrition disorders	1	There was one event of Hyperphosphataemia. Review of this case did not identify any new safety signals.
Nervous system disorders	12	The events include: Ataxia (1), Cerebellar syndrome (1), Chorea (1), Choreoathetosis (1), Convulsion (1), Dizziness (1), Dyskinesia (2), Dystonia (2), Movement disorder (1), Partial seizures (1). Four of the 12 PTs were reported for 1 patient. Review of these cases did not identify any new safety signals.
Renal and urinary disorders	1	The event was Anuria in a 6-year-old male (same patient as described in the Hepatobiliary disorders SOC above). The patient was receiving multiple medications. Limited clinical details were provided. No new safety signal was identified.

SOC	PT Count	Comment
Respiratory, thoracic and mediastinal disorders	2	A 22-month-old female with suspected acute encephalopathy experienced aspiration pneumonia, dyskinesia, and respiratory depression. The patient experienced an apneic attack and intermittent respiratory arrest (10-20 seconds) following extubation. The patient recovered from respiratory depression 2 days after discontinuing fosphenytoin. Based upon the available information, a possible contributory role of the suspected drug fosphenytoin cannot be excluded for the reported events due to implied temporal relationship and improvement of respiratory depression while blood drug levels decreased. However, the patient had underlying acute encephalopathy and was receiving multiple concomitant medications which may have contributed to the reported events. No new safety signals were identified.

Postmarketing Events of Non-serious Cases

Of the 141 fosphenytoin pediatric reports, there were 19 non-serious cases which were not previously discussed in the above safety topics.

Review of the 19 non-serious cases did not identify any new safety signals.

Adult and Pediatric adverse event comparison

In the pediatric studies:

A comparison of AE data from pediatric and adult populations (enrolled in the same and in separate clinical studies)was made by the sponsor.

Treatment of Prophylaxis of Seizures – AEs in Study 982-028 and Study 982-026

To evaluate age-dependent AEs following a fosphenytoin IV loading dose, data from 2 studies (with similar numbers of subjects and administered treatments) were divided into 2 age groups: adults (defined as subjects aged 17 years or older) and pediatric (defined as subjects younger than 17 years). The data for the adult population were derived from Study 982 and those for the pediatric population were derived from the 96 pediatric subjects in Study 982-028 who received fosphenytoin IV.

Data are summarized in Table 15, which lists AEs that were reported in at least 2% of the subjects in either study. The AEs reported for the pediatric and adult populations were generally similar in kind and frequency. At least 1 AE was reported in 64.6% of pediatric subjects compared with 90.0% of adult subjects.

As can be seen in Table 9 (the sponsor's Table 15 from Safety Update), the incidence of some AEs differed between the 2 populations. In pediatric subjects, the AEs reported in at least 10% of pediatric subjects were vomiting, nystagmus, and ataxia, whereas, those in the adult subjects were nystagmus, dizziness, somnolence, ataxia, and pruritus. With the exceptions of pruritus, dizziness, nystagmus, vomiting, somnolence, nervousness, and fever, differences in incidences of specific AEs between the populations were within 4%. Some of the differences may be attributed to AEs expected in pediatrics (e.g., vomiting and fever) and possibly to lesser communication skills in the younger subjects.

Table 9 Comparison of Adverse Events (Reported in at Least 2% of Subjects in Study 982-028) Between Pediatric Subjects in Study 982-028 and Adult Subjects in Study 982-026 by Decreasing Frequency in Study 982-028

Body System Preferred Term	**Pediatric Subjects Study 982-028 N = 96[a] n (%)**	**Adult Subjects Study 982-026 N = 90 n (%)**
Any body system (all AEs)	62 (64.6)	81 (90.0)
Nervous	36 (37.5)	69 (76.7)
Nystagmus	17 (17.7)	40 (44.4)
Ataxia	10 (10.4)	10 (11.1)
Nervousness	7 (7.3)	0 (0.0)
Somnolence	6 (6.3)	18 (20.0)
Agitation	3 (3.1)	3 (3.3)
Tremor	2 (2.1)	3 (3.3)
Dizziness	2 (2.1)	28 (31.1)
Body as a Whole	27 (28.1)	13 (14.4)
Fever	8 (8.3)	1 (1.1)
Injection site pain	4 (4.2)	0 (0.0)
Injection site reaction	4 (4.2)	1 (1.1)
Face edema	4 (4.2)	1 (1.1)
Pain	4 (4.2)	1 (1.1)
Injection site edema	3 (3.1)	0 (0.0)
Injection site inflammation	3 (3.1)	0 (0.0)
Digestive	23 (24.0)	17 (18.9)
Vomiting	20 (20.8)	2 (2.2)
Cardiovascular	13 (13.5)	13 (14.4)
Hypotension	5 (5.2)	7 (7.8)
Bradycardia	3 (3.1)	0 (0.0)
Skin and Appendages	11 (11.5)	45 (50.0)
Pruritus	6 (6.3)	44 (48.9)
Rash	5 (5.2)	1 (1.1)
Special Senses	7 (7.3)	14 (15.6)
Eye disorder	3 (3.1)	1 (1.1)
Respiratory	5 (5.2)	3 (3.3)
Cough increased	2 (2.1)	0 (0.0)
Urogenital	5 (5.2)	2 (2.2)

Body System Preferred Term	**Pediatric Subjects Study 982-028 N = 96[a] n (%)**	**Adult Subjects Study 982-026 N = 90 n (%)**
Hematuria	2 (2.1)	0 (0.0)
UTI	2 (2.1)	1 (1.1)
Hemic and Lymphatic	2 (2.1)	2 (2.2)
Cyanosis	2 (2.1)	0 (0.0)

a. Includes only the 96 subjects in Study 982-028 who received fosphenytoin IV.
Abbreviations: AE = adverse event, n = number of evaluable subjects experiencing each AE; N = total number of subjects; UTI = urinary tract infection
Source: Parke-Davis Clinical Data Summary of Fosphenytoin Therapy in Pediatric Patients, Table 9

A Within-Study comparison of AEs in Adult vs. Pediatric Patients (Study 982-016)

A within-study comparison of AE data from both pediatric and adult populations treated in a single study (982-016) provides useful information. Data from this open-label study evaluated the safety and tolerability of fosphenytoin IV in the acute treatment of subjects (including pediatric subjects aged younger than 5 years) who were being treated for generalized convulsive status epilepticus. Data from this study were divided according to age into 2 groups: those aged 16 years or younger (pediatric population) and those aged older than 16 years (adult population). Due to the small number (N = 10) in the pediatric population, a quantitative comparison between pediatric and adult populations yields little useful information; however, the most commonly reported AEs in both populations are generally similar and differences are primarily attributable to the differences in the AEs often reported in each of the populations. See Table 10 (sponsor's Table 16 from Safety Update).

Table 10 Adverse Events Reported in the Pediatric vs Adult Population in Study 982-016 (in Decreasing Order of Frequency Based on Pediatric Population—All)

Adverse Event	**Pediatric Population[a] N = 10**		**Adult Population[b] N = 63**	
Body System Preferred Term	**All n (%)**	**Related to Study Medication n (%)**	**All n (%)**	**Related to Study Medication n (%)**
Any Adverse Event	7 (70)	5 (50)	52 (82.5)	28 (44.4)
Nervous System				
Somnolence	4 (40)	4 (40)	4 (6.3)	2 (3.2)
Nystagmus	2 (20)	1 (10)	18 (28.6)	16 (25.4)
Ataxia	1 (10)	1 (10)	0 (0)	0 (0)
Personality disorder	1 (10)	1 (10)	0 (0)	0 (0)
Abnormal gait	1 (10)[c]	0 (0)	0 (0)	0 (0)

Adverse Event	Pediatric Population[a] N = 10		Adult Population[b] N = 63	
Body System Preferred Term	**All n (%)**	**Related to Study Medication n (%)**	**All n (%)**	**Related to Study Medication n (%)**
Hemiplegia	1 (10)[c]	0 (0)	0 (0)	0 (0)
Paralysis	1 (10)[c]	0 (0)	1 (1.6)	0 (0)
Body as a Whole				
Abdominal pain	1 (10)	1 (10)	1 (1.6)	0 (0)
Headache	1 (10)	1 (10)	9 (14.3)	2 (3.2)
Digestive System				
Vomiting	3 (30)	1 (10)	5 (7.9)	4 (6.3)
Skin and Appendages				
Pruritus	2 (20)	2 (20)	4 (6.3)	4 (6.3)

a. Table only includes adverse events that reported in pediatric subjects and corresponding adverse events in adult subjects.
b. In this study, the adult population was defined as being older than aged 16 years.
c. These adverse events were reported in a single subject (14-year-old male) who was diagnosed with probable Todd's Paralysis.
Abbreviations: n = number of evaluable subjects experiencing each AE; N = total number of subjects
Source: Parke-Davis Clinical Data Summary of Fosphenytoin Therapy in Pediatric Patients, Table 10

In postmarketing reports:

Table 11 (sponsor's Table 21 from Safety Update) compares summary data for postmarketing reports in the pediatric and adult patient populations.

Table 11 Comparison of Pediatric and Adult Patients for Fosphenytoin Event Tabulations and Reporting Percentages Through 31 March 2015 by MedDRA SOC

MedDRA SOC	Pediatric		Adult		Ratio
	No. of Cases	**No. of Events**	**No. of Cases**	**No. of Events**	**Pediatric/ Adult**
Blood and lymphatic system disorders	10 (7.09%)	15	28 (7.76%)	35	0.91
Cardiac disorders	27 (19.15%)	40	85 (23.55%)	136	0.81
Congenital, familial and genetic disorders	0	0	2 (0.55%)	2	0
Ear and labyrinth disorders	2 (1.42%)	2	9 (2.49%)	9	0.57
Endocrine disorders	1 (0.71%)	1	2 (0.55%)	2	1.3
Eye disorders	2 (1.42%)	2	7 (1.94%)	7	0.73
Gastrointestinal disorders	10 (7.09%)	13	20 (5.54%)	30	1.3
General disorders and administration site conditions	51 (36.17%)	54	82 (22.71%)	109	1.6

MedDRA SOC	Pediatric		Adult		Ratio
	No. of Cases	No. of Events	No. of Cases	No. of Events	Pediatric/ Adult
Hepatobiliary disorders	5 (3.55%)	5	35 (9.70%)	43	0.37
Immune system disorders	1 (0.71%)	1	11 (3.05%)	11	0.23
Infections and infestations	4 (2.84%)	4	28 (7.76%)	54	0.37
Injury, poisoning and procedural complications	43 (30.50%)	58	42 (11.63%)	57	2.62
Investigations	42 (29.79%)	58	111 (30.75%)	185	0.97
Metabolism and nutrition disorders	11 (7.80%)	16	11 (3.05%)	20	2.56
Musculoskeletal and connective tissue disorders	2 (1.42%)	2	12 (3.32%)	20	0.43
Nervous system disorders	32 (22.70%)	54	87 (24.10%)	151	0.94
Psychiatric disorders	3 (2.13%)	6	24 (6.65%)	39	0.32
Renal and urinary disorders	4 (2.84%)	5	21 (5.82%)	28	0.49
Reproductive system and breast disorders	1 (0.71%)	1	3 (0.83%)	5	0.86
Respiratory, thoracic and mediastinal disorders	10 (7.09%)	14	35 (9.70%)	58	0.73
Skin and subcutaneous tissue disorders	16 (11.35%)	19	60 (16.62%)	80	0.68
Social circumstances	0	0	2 (0.55%)	2	0
Surgical and medical procedures	2 (1.42%)	2	4 (1.11%)	8	1.28
Vascular disorder	14 (9.93%)	15	55 (15.24%)	63	0.65

A comparison of preferred terms reporting proportions $\geq$ 3 for pediatric compared to adult patients is presented in Table 12 (sponsor's Table 22 in Safety Update). In general, there were many preferred terms reported for the adult patient population that were not reported for the pediatric population. The higher number of preferred terms associated with adult cases may be due to concurrent illnesses and/or co-morbidities present in adult patients which are not present in pediatric patients.

Although the number of reports in the adult population is approximately 2.5 times greater than the pediatric population, for 7 preferred terms from the pediatric population the reporting ratios were at least 3 times higher in pediatric patients than adults.

Table 12 Summary of Preferred Term Reporting Proportion 3 Times Greater in Pediatric Patients (n=141) versus Adult Patients (n=361)

System Organ Class	Preferred Term	Pediatric Number of Cases (% of Cases)	Adult Number of Cases (% of Cases)	Ratio of Pediatric / Adult Cases
General disorders and administration site conditions	Drug ineffective	20 (14.18%)	13 (3.60%)	3.9
Injury, poisoning and procedural complications	Accidental overdose	16 (11.35%)	7 (1.94%)	5.6
Injury, poisoning and procedural complications	Intentional overdose	6 (4.26%)	4 (1.11%)	3.8
Injury, poisoning and procedural complications	Drug administration error	5 (3.55%)	3 (0.83%)	4.3
Investigations	Drug level below therapeutic	5[a] (3.55%)	0	3.55
Investigations	Drug level increased	4 (2.84%)	2 (0.55%)	5.2
Metabolism and nutrition disorders	Hyperglycaemia	5 (3.55%)	1 (0.28%)	12.7

a. Case 2004093197 reported Drug level below therapeutic for temazepam; therefore, there were 5 fosphenytoin cases reporting Drug level below therapeutic.

A comparison of pediatric and adult postmarketing adverse event ratios did not identify any new safety signals in the pediatric patient population compared to adults.

Medication Errors and Overdosages

Review of the clinical trial data did not identify any reports of medication errors or overdoses occurring in the pediatric patient population.

Forty-two cases were identified in the postmarketing dataset. Three of the 42 cases involved overdoses with drugs other than fosphenytoin. In the remaining 39 cases, 3

cases involved non-overdose medications errors, 1 case involved an underdose and the remaining 35 cases involved reported overdoses.

The most frequently reported reasons for these 35overdose cases were incorrect dose administered [no specific reason provided] (16), dose calculation error (5), and product label confusion (5). In the 5 dose calculation error cases, 2 cases involved errors related to incorrect placement of decimal points; 1 case used weight in pounds for calculations instead of kilogram weight; in another case the vial mg/mL volume was incorrectly entered into the hospital's software; in the fifth case the dose was calculated for continuous infusion instead of 3 divided doses. In the product label confusion cases, either the vial volume was incorrectly read or there was confusion between the fosphenytoin mg dose and phenytoin equivalent (PE) dose.

In the Safety Update, the sponsor lists three risk mitigation measures used in the United States to address medication errors taken over the years since the approval of fosphenytoin in 1996.

- 1999: Vial packaging in the United States (US) was revised to emphasize the total phenytoin equivalent units (PE) in the vial, and reminder stickers reinforcing the total PE in each vial were added to existing stock.

- 1999: A Dear Healthcare Professional (DHCP) letter was sent, carton and vial labels in the US were revised to emphasize the total phenytoin equivalent units (PE) in the vial, and reminder stickers reinforcing the total PE in each vial were added to existing stock. In addition, hospital sales representatives visited hospital pharmacists at major centers to emphasize the total PE/vial.

- 2009: A DHCP letter was issued informing US healthcare professionals that potentially fatal dosing errors continued to occur with fosphenytoin. The letter stated that if care is not taken the concentration may be mistaken for the total amount in the vial and that this has led to significant overdoses. The letter noted 7 cases reported to the FDA MedWatch system where young children received overdoses of fosphenytoin and died. The letter notes that fosphenytoin is not approved for use in pediatric patients in the US.

In addition, the sponsor notes that in the United States the fosphenytoin labeling was updated with a Boxed Warning regarding cardiovascular risks associated with rapid infusion rates, with text in the Dosage and Administration section about the use of phenytoin sodium equivalents, and with extensive text in the Warnings section discussing avoidance of confusion between the amount of drug in the vial and the concentration of the drug in the vial. The carton and vial labels were also modified to decrease this content vs. concentration confusion. The sponsor states that the number of reported cases of medication error and drug overdose in the United States has decreased in the time period from 2002 to 2015 compared to 1997 to 2001.

Reviewer Note:

The estimation of the effectiveness of these risk mitigation measures in the United States may be confounded by the fact that, as noted another section of the Safety Update, Pfizer did not market Cerebyx in the United States from 30 September 2010 through 29 October 2013.

If this pediatric supplement is approved, the inclusion of pediatric dosing in the labeling would be expected to help reduce medication error.

Further enhanced pharmacovigilance in the future regarding medication error with fosphenytoin (particularly with pediatric patients) should be considered to confirm that the current risk mitigation measures are adequate.

9 Appendices

9.1 Literature Review/References

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Ogutu BR, Newton CRJC, Muchohi SN, et al. Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus. *Br J Clin Pharmacol* 2003: 56; 112–119.

9.2 Labeling Recommendations

See Approval letter for negotiated changes and PLR conversion of the CEREBYX labeling.

9.3 Advisory Committee Meeting

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHILIP H SHERIDAN
02/16/2017

TERESA J BURACCHIO
02/16/2017