Cross-Discipline Team Leader Review

Date	February 18, 2017
From	Teresa Buracchio, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	0204500 Supplement 003
Applicant	Parke Davis, a division of Pfizer
Date of Submission	9/1/2016
PDUFA Goal Date	3/1/2017
Proprietary Name / Non-Proprietary Name	Cerebyx (Fosphenytoin Sodium Injection)
Dosage form(s) / Strength(s)	Intravenous (IV); 100 mg PE per 2 mL vial (50 mg PE per mL); 500 mg PE per 10 mL vial (50 mg PE per mL)
Applicant Proposed Indication(s)/Population(s)	1. Pediatric Generalized Tonic Clonic Status Epilepticus 2. Seizures during Pediatric Neurosurgery 3. Short-term Substitution for Oral Phenytoin for Pediatric Patients
Recommendation on Regulatory Action	Approval

1. Background

Cerebyx (fosphenytoin sodium injection) is a prodrug of phenytoin administered by intravenous (IV) or intramuscular injection (IM). Upon administration, Cerebyx is rapidly and completely converted to phenytoin. Cerebyx is administered in terms of "mg phenytoin equivalent" (mg PE) as 1 mole of fosphenytoin is metabolized into 1 mole of phenytoin. Formulation characteristics of Cerebyx (e.g., more neutral pH (8.6 to 9) and increased water solubility) allow for a more rapid infusion rate and decreased potential for local tissue destruction compared to IV phenytoin. Cerebyx was approved for use in 1996. Current indications for Cerebyx in adults include:

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

This submission seeks to expand the label to include pediatric age groups (birth to 16 years) to the current approved indications in adults. Additionally, this submission will convert the current prescribing information (PI) to Physician Labeling Rule (PLR) format.

This supplement is a resubmission that was originally submitted on December 21, 1998. The submission contained data from 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. The submission was assessed as providing incomplete information to inform pediatric dosing and a Complete Response letter was issued on October 21, 1999.

Using data from the prior submission along with some additional pediatric PK data obtained from another study, the sponsor has proposed and completed a modeling and simulation approach to develop a pediatric dosing regimen. There were several meetings between the sponsor and FDA to discuss the acceptability of this approach. A more detailed overview of those meetings can be found in the Clinical Pharmacology review by Dr. M. Bewernitz. A pre-sNDA meeting was held on December 11, 2015 to discuss the contents of this submission.

2. Product Quality

The quality reviewers were Drs. L. Soldatova and D. Lewis. There was no new CMC information included in this submission; however, the reviewers had comments regarding the CMC-related sections of the PI.

The current label has an equivalency statement between fosphenytoin sodium and phenytoin sodium on the current vial and carton labels and in the Section 11 and Section 16 of the PI. The label does not include an equivalency statement linking the quantity of fosphenytoin sodium to fosphenytoin (as required by the USP and FDA Salt Nomenclature Policy). With input from both the clinical reviewer and DMEPA, CMC agrees that the additional

equivalency statement linking the quantity of fosphenytoin sodium to fosphenytoin should not be added since the product has been labeled in terms of fosphenytoin sodium for many years and a change in this information could be confusing for prescribers. The quality reviewers also suggested revisions to the vial and container labels that were accepted by the sponsor, and the revised labels were found to be acceptable by DMEPA.

The quality review team recommends approval of the supplement. I agree with their recommendations.

3. Nonclinical Pharmacology/Toxicology

No new data submitted or required.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by Dr. M. Bewernitz with Team Leaders Dr. K. Krudys and Dr. A. Men.

The sponsor developed a population pharmacokinetic (PK) model to inform dosing for pediatric patients using PK data obtained from the following sources:

- Study 982-016 Open-Label, Rate- Escalation Multicenter Study to Assess Safety, Tolerance, and Pharmacokinetics of Intravenously Administered Fosphenytoin Sodium (CI-982) in the Acute Treatment of Generalized Convulsive Status Epilepticus; Total N = 85, Pediatric N = 10 (5-14 years)
- Study 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 years) (Neonates, n = 21, Infants, n = 33, Children, n = 45, Adolescents, n = 14)
- Phenytoin PK data provided by the author of a literature study (Ogutu et al., 2003)[1]

The Clinical Pharmacology review also used data from the following study to assess infusion rates:

- Study 982-024: Randomized, open-label, 3-way crossover study to assess the PK of loading doses of IV fosphenytoin 1200 mg PE infused at 100 mg PE/min, IV fosphenytoin 1200 mg PE infused at 150 mg PE/min, and IV phenytoin 1200 mg infused at 50 mg/min to n=12 healthy adult men.

4.1. Status Epilepticus Loading Dose

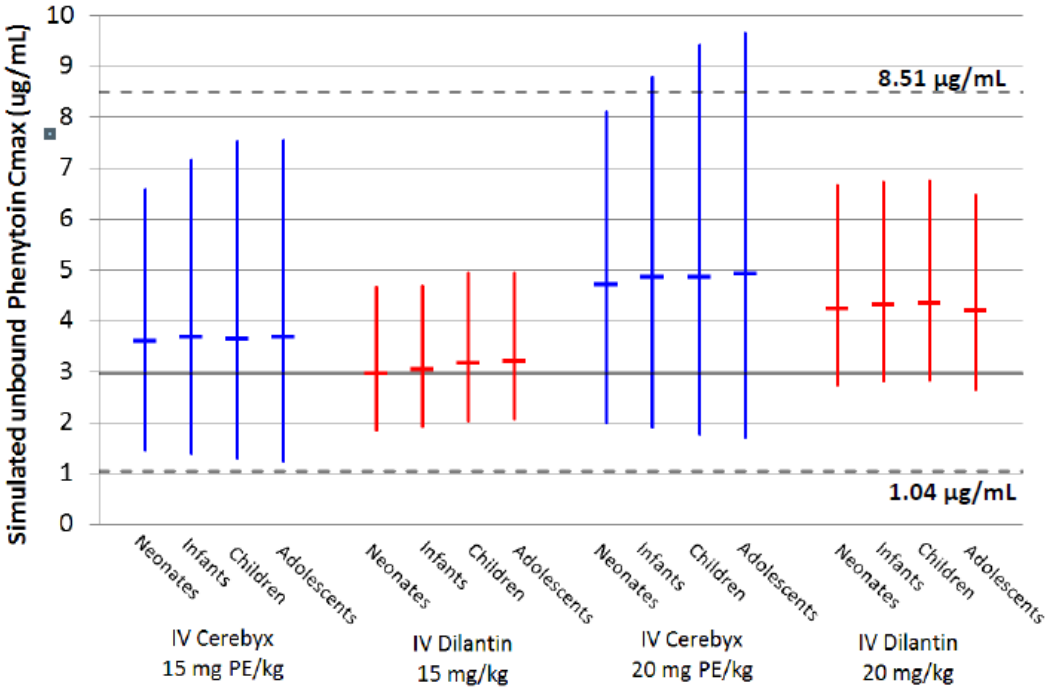
As described in Dr. Bewernitz's review, the sponsor conducted extensive pharmacokinetic modeling and simulation to generate a combined fosphenytoin and phenytoin population

[1]Ogutu BR, Newton CR, Muchohi SN, Otieno GO, Edwards G, Watkins WM, Kokwaro GO. Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus. Br J Clin Pharmacol. 2003 Jul;56(1):112-9.

pharmacokinetic model of pediatric unbound phenytoin concentration. The Division had advised the sponsor to focus on unbound phenytoin C_{max} for developing a model for a loading dose for status epilepticus as C_{max} is the driving factor in resolution of seizures. In order to evaluate the simulated pediatric fosphenytoin loading doses, the sponsor derived a "reference range" of unbound phenytoin C_{max} values based on observed unbound phenytoin concentrations in adults receiving IV Cerebyx in Study 0982-016. 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 conducted PK simulations of various loading dose levels in virtual pediatric patients and proposed a loading dose that fell within the molar equivalent of the adult exposure reference range. Based on this analysis, the sponsor proposed a loading dose of 15 mg PE/kg for status epilepticus in pediatric patients.

Upon review, Dr. Bewernitz noted that the sponsor's proposed reference range included adults who received Cerebyx loading doses outside of the approved dose range and also some pediatric patients. After excluding those patients, Dr. Bewernitz developed a "revised reference range" of 1.04 to 8.51 μg/mL that was higher than the sponsor's proposed reference range. Based on the revised range, the sponsor's simulations for both 15 mg PE/kg Cerebyx and 20 mg PE/kg Cerebyx administered to virtual pediatric patients appeared to produce comparable unbound phenytoin exposures to adult Cerebyx exposures and to pediatric IV Dilantin (phenytoin) exposures These findings are demonstrated in the figure below which is copied from Dr. Bewernitz's review. The matching of unbound phenytoin exposures to adult and pediatric patients provides a bridge to prior findings of effectiveness with IV Dilantin in the pediatric population and Cerebyx in the adult population.

Figure 1. Simulated Unbound Phenytoin C_{max} 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 C_{max} values following IV Cerebyx administration to virtual pediatric patients and red represents simulated unbound phenytoin C_{max} values following IV Dilantin administration to virtual pediatric patients.

Based on these simulations and discussions with the clinical reviewer regarding the safety of the 15 mg PE/kg and 20 mg PE/kg loading doses for status epilepticus, the OCP review team recommends a pediatric loading dose for fosphenytoin for status epilepticus for all pediatric age groups (neonates, infants, children, and adolescents) of 15-20 mg PE/kg.

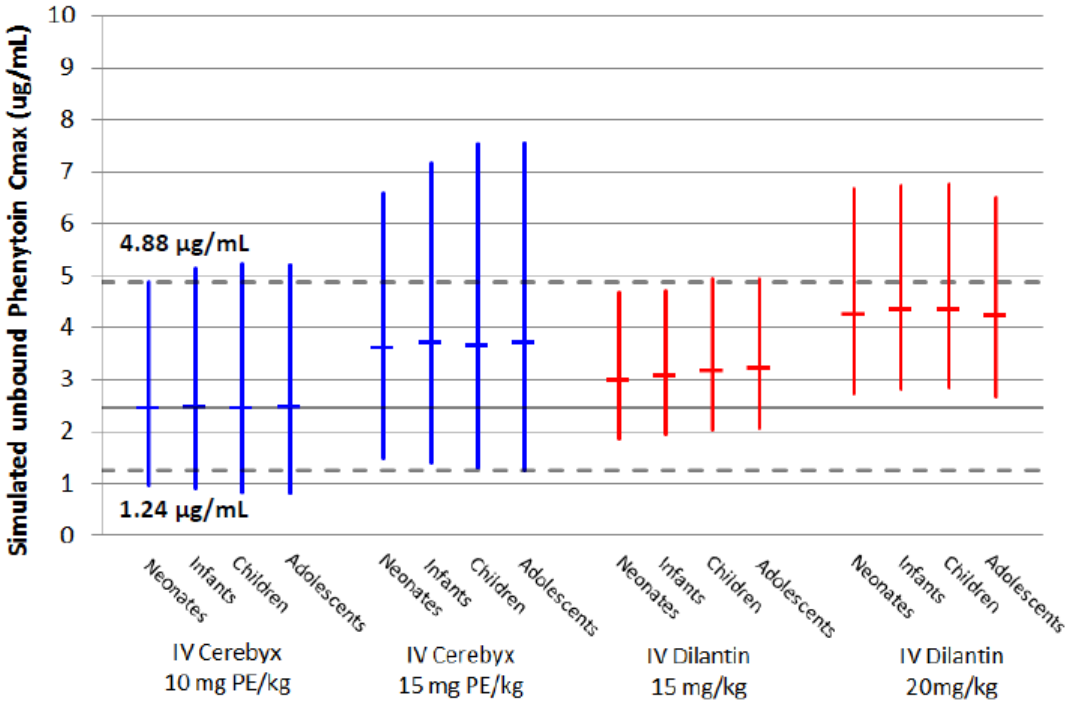
4.2. Non-emergent Loading Dose

The sponsor did not conduct analyses regarding a non-emergent loading dose. The sponsor has proposed a 10-15 mg PE/kg non-emergent Cerebyx loading dose for pediatric patients based on the rationale that a lower dose is appropriate for the non-emergent scenario where it is not critical to obtain a high C_{max}.

Dr. Bewernitz conducted an independent analysis to assess the non-emergent pediatric Cerebyx loading dose using the same methodology that was used for assessing the status epilepticus loading dose. A "revised reference range" of unbound phenytoin C_{max} values (90% PI 1.24– 4.88 µg/mL) was determined based on PK data acquired from adults that received the labelled Cerebyx non-emergent loading dose for Cerebyx (10 – 15 mg PE/kg).

Simulations of unbound phenytoin C_{max} values resulting from 10 mg PE/kg and 15 mg PE/kg loading doses in virtual pediatric patients were similar to the "revised reference range" for adults and to pediatric IV Dilantin (phenytoin) exposures at the 15mg dose. This finding is demonstrated in the figure below which is copied from Dr. Bewernitz's review.

Figure 2. 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 C_{max} values following IV Cerebyx administration to virtual pediatric patients and red represents simulated unbound phenytoin C_{max} values following IV Dilantin administration to virtual pediatric patients.

Based on these simulations, the OCP review team recommends a pediatric loading dose for fosphenytoin for nonemergent situations for all pediatric age groups (neonates, infants, children, and adolescents) of 10-15 mg PE/kg.

4.3. Maintenance Dosing

The current Cerebyx label lists a therapeutic range of 1-2 µg/mL unbound phenytoin. The sponsor used this therapeutic range as a target range to assess the appropriateness of simulated pediatric maintenance dose regimens.

The sponsor used PK simulations for several loading doses (10, 15, and 20 mg PE/kg) followed by 5 days of maintenance dosing at 2, 3, 4, 5, and 6 mg PE/kg/12 hours. These dose levels and dose intervals are based on adult labeled Cerebyx doses (2 and 3 mg PE/kg/12

hours; listed in Cerebyx label as 4-6 mg PE/kg/day) and doses achieved in pediatric Cerebyx trials (2, 3, 4 mg PE/kg/12 hours). The sponsor assessed the proportion of patients with unbound phenytoin C_{trough} values that were within the labelled therapeutic range (1-2 μg/mL) for each of the dosing regimens.

Since the current labels for Cerebyx and phenytoin recommend drug monitoring to guide maintenance dosing, the sponsor expected that drug monitoring would also be utilized in pediatric patients. Therefore, they proposed to use the simulated unbound phenytoin C_{trough} values from Day 2 to assess the performance of the different maintenance regimens.

The sponsor's analysis of the various dosing regimens showed that only approximately 60% of patients could be expected to have a Day 2 C_{trough} within the labelled 1-2 μg/mL therapeutic range of unbound phenytoin. Per discussions with Dr. Bewernitz, this is likely due to high variability in the PK data for phenytoin and the narrow therapeutic range that was designated. The various regimens appeared to perform similarly. The sponsor's conclusion was that fixed maintenance dosing was not appropriate for pediatric patients and that therapeutic drug monitoring would be necessary to guide the selection of maintenance dosing. The sponsor proposed a maintenance dose level of 2-4 mg PE/kg/12 hours with therapeutic drug monitoring to guide further maintenance dosing. The OCP review team agreed with the sponsor's proposal.

4.5. Rate of infusion

Loading dose

The sponsor is recommending an infusion rate of 2 mg PE/kg/minute (max 150 mg PE/minute) for loading doses in status epilepticus and in non-emergent situations. This rate is within the ranges of those used in the pediatric clinical studies that provided data for the PK simulations, Study 982-028 and 982-016. No safety signals were identified with those rates of infusion (refer to the clinical safety review by Dr. Sheridan discussed in Section 7). In the PK simulations, the infusion rate of 2 mg PE/kg/minute (maximum 150 mg PE/minute) was used. The 150 mg PE/minute rate is the upper limit for adults in the current approved Cerebyx label. The Cerebyx label also indicates that monitoring cardiovascular and respiratory status is necessary during intravenous administration of Cerebyx. These same recommendations will remain in place for pediatric patients. The OCP review team agrees with the proposed infusion rate of 2 mg PE/kg/minute (max 150 mg PE/minute) for loading doses of Cerebyx.

Maintenance dose

The sponsor is recommending an infusion rate of 1-2 mg PE/kg/minute (max 100 mg PE/minute) for all maintenance dosing. This infusion rate is lower than what was used in the pediatric clinical studies described above. The sponsor is recommending a slower rate based on adverse events of vomiting and nystagmus that have been reported with infusion rates > 3 mg/kg/min and/or doses > 20 mg/kg. Dr. Bewernitz notes that AUC is comparable between the 100 and 150 mg PE/min infusion rates in study Study 982-024; however the 150 mg PE/minute infusion rate is expected to produce a 14% higher unbound C_{max} than the 100 mg

PE/kg infusion rate. Because obtaining a high C_{max} is not critical with maintenance dosing, the OCP review team finds this proposal acceptable.

4.6. Dosing in patient subgroups

The current Cerebyx and Dilantin labels indicate the monitoring of unbound phenytoin concentration may be useful in patients with hypoalbuminemia. The sponsor has reviewed the published literature to determine if this recommendation is also applicable to the pediatric population. The literature indicates that there is a trend for reduced unbound phenytoin concentrations accompanying an increase in albumin concentration in children. The OCP review team agrees with the sponsor's additions to the label regarding hypoalbuminemia.

The OCP review team has concluded that evidence presented in literature reports (b) (4) do not support a dose adjustment of Cerebyx based on bilirubin levels.

Based on the results of the simulations described above, the OCP review team agrees that a weight-based approach for pediatric dosing is acceptable.

The following table copied from Dr. Bewernitz's review summarizes the key dosing recommendations from OCP which are to be reflected in the Cerebyx PI. I agree with their recommendations.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	2 pediatric clinical trials combined with PK modeling and simulation.
General dosing instructions	CEREBYX should ordinarily not be given intramuscularly. Loading Dose: • *Status epilepticus*: 15-20 mg PE/kg loading dose • *Non-emergent situations*: 10-15 mg PE/kg loading dose • If IV administration, recommended infusion rate is 2 mg PE/kg/min (max 150 mg PE/kg/min) Maintenance Dose: • *Initial dose*: 2-4 mg PE/kg to be given 12 hours after loading dose • *Subsequent doses*: Therapeutic drug monitoring is recommended in order to guide subsequent maintenance doses (as is the case for adult fosphenytoin therapy and phenytoin therapy). Dosing interval is 12 hours. • If IV administration, recommended infusion rate is 1-2 mg PE/kg/min (max 100 mg PE/kg/min)
Dosing in patient subgroups (intrinsic and extrinsic factors)	Similar to adults, doses are to be administered on a weight basis and monitoring is recommended for renal and/or hepatic impairment or hypoalbuminemia.

5. Clinical Microbiology

No new data submitted or required.

6. Clinical/Statistical- Efficacy

Efficacy studies were not required for the adult indications or for this pediatric submission. After administration, fosphenytoin is completely and rapidly cleaved to phenytoin (the active moiety). Clinical efficacy is based on the prior demonstration of efficacy of Phenytoin Injection which has been approved in the US since 1956 for both pediatric and adult patients for the same indications now requested for fosphenytoin in pediatric patients. Matching unbound phenytoin exposures between pediatric patients administered IV Cerebyx and pediatric patients administered IV Dilantin provides a bridge to prior findings of effectiveness with IV Dilantin in the pediatric population. Additional supportive information includes comparable exposures with IV Cerebyx administered to adults.

The modeling and simulation approach was used to provide pediatric dosing recommendations. Refer to Section 4 for a more detailed discussion of this approach.

7. Safety

The safety data in this submission was reviewed by Dr. P. Sheridan, DNP clinical reviewer.

Safety data from 133 pediatric subjects in seven clinical studies were reviewed for this submission.

- Study 982-014 Open-Label, Multicenter Study of the Safety and Tolerance of Intramuscularly Administered, Multiple Dose Fosphenytoin in Hospitalized Neurosurgery; Total N = 118; Pediatric N = 2 (both 16 years)
- Study 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 years)
- Study 982-016 Open-Label, Rate- Escalation Multicenter Study to Assess Safety, Tolerance, and Pharmacokinetics of Intravenously Administered Fosphenytoin Sodium (CI-982) in the Acute Treatment of Generalized Convulsive Status Epilepticus; Total N = 85, Pediatric N = 10 (5-14 years)
- Study 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 years)
- Study 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 years)
- Study 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 years) (Neonates, n = 21, Infants, n = 33, Children, n = 45, Adolescents, n = 14)

- Study 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 years)

The majority of the subjects for the safety analysis 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). This was an open-label study which limits interpretation of the safety data; however, as Dr. Sheridan notes in his review, there is a long history of use of phenytoin and fosphenytoin both in adult and children (off-label) which indicates the at fosphenytoin can be used safely in the proposed doses and rates of infusion proposed for the pediatric population.

7.1. Deaths

There were two deaths that occurred in these studies:

- Study 982-014, Center 001, Subject Number 014: The patient was a 16 year-old male with severe closed head injury secondary to a motor vehicle accident. The patient died on Study Day 5 from brain herniation due to an increase in intracranial pressure.
- Study 982-028, Center 004, Subject Number 007: The patient was an 11-day-old premature female who was hospitalized for Escherichia coli sepsis and meningitis. The patient died on Study Day 1 from cardiac arrest. The patient had marked hemodynamic instability requiring maximum medical support. The patient's hemodynamic status declined further following infusion of fosphenytoin.

Both deaths were assessed by study investigators as unrelated to fosphenytoin. Dr. Sheridan agrees that these deaths appear to be related to underlying morbidity and not to fosphenytoin.

7.2. Nonfatal Serious Adverse Events

There were no nonfatal SAEs reported. Fatal SAEs are described above.

7.3. Dropouts and Discontinuations

There were five patients withdrawn from the studies and, of these, three patients were discontinued due to adverse events. Two of the three subjects were previously described in Section 7.1 above. The third subject was withdrawn for an adverse event of elevated plasma phenytoin concentrations which was considered mild and nonserious.

7.4. Common Adverse Events

As noted in Dr. Sheridan's review, approximately two-thirds of the 133 pediatric subjects experienced at least one adverse event and approximately 40% of subjects experienced at least 1 adverse event considered possibly associated with the study medication. Most adverse events were mild or moderate in severity.

The most frequently reported adverse events that were reported in at least 5% of subjects in the pediatric subjects were nystagmus, vomiting, ataxia, fever, somnolence, nervousness, and pruritus. These adverse events are similar to what has been reported in the adult population.

7.5. Adverse Events of Interest

A potential safety concern identified with Cerebyx is the relationship between high unbound phenytoin levels following a loading dose with the occurrence of cardiovascular adverse events, particularly hypotension and arrhythmia. Dr. Sheridan reviewed reports of cardiovascular adverse events that occurred in 14 subjects in Study 982-028. Pharmacokinetic data was available for 9 of the 14 subjects. The only cardiovascular adverse event that was associated with high unbound phenytoin was the previously described fatality in a critically ill neonatal infant.

Additionally, Dr. Sheridan identified 8 patients with high unbound phenytoin concentrations (upper 90% bound and greater than or equal to 7.47 μg/mL) in Study 982-028 and assessed the occurrence of adverse events in those patients. There were no additional cardiovascular adverse events identified. Reported adverse events included vomiting and nystagmus which can be seen with lower phenytoin levels.

Based on this assessment, Dr. Sheridan did not identify an increased risk of cardiovascular adverse events associated with high unbound phenytoin levels.

7.6. Laboratory Findings/Vitals/ECG

Available data was reviewed from Study 982-028. There were no notable trends in laboratory values identified. Modest reductions in mean blood pressure and respiratory rate were noted with both IV and IM administration. No cardiac arrhythmias were reported.

7.7. Safety by Age Group

Dr. Sheridan reviewed the safety data by age group within Study 982-028 and found no notable differences in safety by pediatric age group.

Dr. Sheridan also did several additional evaluations comparing safety data in pediatric patients vs. adults between Study 982-028 and 982-026, within Study 982-016, and in the postmarketing data. He found no new safety signals in the pediatric population.

7.8. Postmarket Experience

In the pre-sNDA meeting minutes from December 2015, the Division recommended that the sponsor focus on a number of adverse events of special interest (e.g., cardiovascular events, hypotension, anticonvulsant serum plasma levels, etc.) in the postmarket safety review. Please refer to Dr. Sheridan's review for a detailed description of those safety analyses. Of these items, Dr. Sheridan identified only Medication Errors and Overdose as an area of potential concern. There were 35 cases of overdose with the most frequently reported reasons

being incorrect dose administered (16), dose calculation error (5), and product label confusion (5). There have also been some fatalities associated with fosphenytoin overdoses and/or medication errors. The sponsor has taken risk mitigation strategies since Cerebyx approval in 1996 to address these issues that includes changes to product packaging, two Dear Healthcare Provider letters, and a Boxed Warning regarding cardiovascular risks associated with rapid infusion.

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; however, Dr. Sheridan notes that this apparent decrease may be confounded by the fact that Cerebyx was not marketed in the United States from September 30, 2010 through October 29, 2013. The approval of this supplement with dosing recommendations for pediatric patients should help to reduce medication errors.

These finding were discussed with the Safety Team Leader, Dr. Sally Yasuda, who recommended that we request postmarketing surveillance and enhanced pharmacovigilance for overdoses resulting from medication errors in the approval letter.

8. Advisory Committee Meeting

None required.

9. Pediatrics

The submission was discussed with the Pediatric Review Committee and there were no pediatric issues identified.

10. Labeling

The label was converted to PLR format. Please see final Label and discussions in the above review.

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval.

- Risk Benefit Assessment: Based on PK data and the need of achieving higher exposure levels of Cerebyx to quickly treat status epilepticus, the benefits of a loading dose of 15-20 mg PE/kg for Cerebyx in pediatric patients outweigh the risks. However, there is not an urgent need to rapidly achieve high Cerebyx exposures for non-emergent treatments; therefore, a lower loading dose of 10-15 mg PE/kg is recommended. A maintenance dose level of 2-4 mg PE/kg/12 hours for Cerebyx with therapeutic drug monitoring to guide further maintenance dosing will allow for exposures to be maintained in a target range

that has been shown to have adequate safety and efficacy in adults. The safety and PK data submitted support the extension of the current indications in adults to the pediatric age groups of birth to 17 years.

Postmarketing surveillance and enhanced pharmacovigilance for overdoses resulting from medication errors will be requested in the approval letter.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies: None required.

- Recommendation for other Postmarketing Requirements and Commitments: None.

- Recommended Comments to Applicant: The Clinical Team has none.

APPEARS THIS WAY ON ORIGINAL

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

/s/

TERESA J BURACCHIO
02/28/2017