CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210864Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA#	NDA 210864/eCTD 0029
EDR location(s)	\\CDSESUB1\evsprod\NDA210864\0029
Submission Date(s)	05/08/2020
PDUFA Goal Date(s)	11/08/2020
Submission Type	Class 2 NDA resubmission
Product Name	Sesquient (Captisol®-Enabled Fosphenytoin Sodium Injection) (CE-Fosphenytoin)
Dosage Form	500 mg PE (phenytoin equivalent) per 10 mL or 100 mg PE per 2 mL sterile solution essentially free of visible particulates in single-dose vials
Dosage Regimen	For status epilepticus: *Adult* loading dose is 15 to 20 mg PE/kg at a rate of 100 to 150 mg PE/min. For non-emergent loading and maintenance dosing: *Adult* loading dose is 10 to 20 mg PE/kg given intravenously; initial maintenance dose is 4 to 6 mg PE/kg/day in divided doses. *Pediatric* loading dose is 10 to 15 mg PE/kg; initial maintenance dose is 2 to 4 mg PE/kg every 12 hours. Administration rate in *pediatric* patients may not exceed 0.4mg PE/kg/min.
Indication	Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery.
Applicant	Sedor Pharmaceuticals, LLC
OCP Division	Division of Neuropsychiatric Pharmacology (DNP)
OND Division	Division of Neurology-II (DN-II)
OCP Reviewer	Adarsh Gandhi, Ph.D. (Clinical Pharmacology)
OCP Team Leader	Angela Men, M.D., Ph.D. (Clinical Pharmacology)

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1. EXECUTIVE SUMMARY

On May 22, 2018, Sedor Pharmaceuticals, LLC submitted its 505(b)(2) NDA for Sesquient. Sesquient (Captisol®-enabled (CE) fosphenytoin sodium) is a novel fosphenytoin formulation containing Captisol®. The applicant is seeking approval for Sesquient based on the safety and efficacy findings from approved Cerebyx® (the reference listed drug, NDA 020450). Sesquient is proposed for same indications as Cerebyx®: for treatment of generalized tonic-clonic status epilepticus and for the prevention and treatment of seizures occurring during neurosurgery. Sesquient differs from Cerebyx® in that Sesquient is formulated with Captisol®, chemically known as sulfobutyl ether beta-cyclodextrin (*i.e.*, Betadex Sulfobutyl Ether Sodium, NF), which (b) (4) (b) (4) room temperature storage instead of refrigerated conditions. No efficacy studies have been conducted with this product.
The Office of Clinical Pharmacology (OCP) had previously reviewed two Phase 1 relative bioequivalence studies (Study 20-A98-AU (CE-Fosphenytoin vs. Cerebyx® after intravenous (IV) administration) and Study 20-247-SA (CE-Fosphenytoin vs. Cerebyx® after intramuscular (IM) administration). The OCP review (dated 03/15/2019) concluded that Sesquient and Cerebyx® are bioequivalent after both IV and IM dosing in healthy volunteers.

However, on March 22, 2019 and December 20, 2019, Complete Response letters (CRL) were sent to Sedor for product quality issues, lack of adequate information to support the safety of Captisol®, and regulatory issues regarding notice of Paragraph IV certification to Cydex Pharmaceuticals. In this review cycle (considered as a Class 2 resubmission), the applicant is seeking approval for Sesquient after addressing FDA's concerns from the CRL.

This review addresses the safety issues of Captisol® in renal impairment patients. As Captisol® is solely eliminated by the kidneys, safety of Captisol® in renal impairment patients is critical. The information submitted in Captisol® Type V DMF 14364 and Captisol® containing approved product, Carnexiv™ (NDA 206030) was used to make dosing recommendations for IV Sesquient in patients with varying degrees of renal impairment. Based on the clinical information in DMF 14364 and NDA 206030, it was concluded that IV Sesquient is safe to be dosed at the same dose and infusion rate in mild (estimated glomerular filtration rate [eGFR] 50-80 mL/min/1.73 m^2), moderate (eGFR >30 to <50 mL/min/1.73 m^2) and severe (eGFR ≤30 mL/min/1.73 m^2) renal impairment patients with close monitoring of serum creatinine levels in severe renal impairment patients (see section 8.6 of prescribing information (PI) of Sesquient).

Dosing recommendation for IM Sesquient cannot be made at this time as the safety of total Captisol® dose at the proposed IM Sesquient dosing has not been established.

1.1. Recommendation

The OCP has reviewed the submitted information contained in NDA 210864/SD#0029 and finds them acceptable from a clinical pharmacology perspective. The OCP recommends approval of Sesquient IV injection for treatment of generalized tonic-clonic status epilepticus and for the prevention and treatment of seizures occurring during neurosurgery (see Table 1 for dosing regimen). Only close monitoring of serum creatinine for severe renal impairment patients is

recommended and no dose adjustment for Sesquient IV injection is needed in mild, moderate or severe renal impairment patients.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of safety and/or efficacy	Please refer to the Clinical Pharmacology review on PK bridging study between IV and IM formulations of Sesquient and Cerebyx® in healthy volunteers.
Safety issues	There is insufficient safety data to support the same infusion rate of IV formulation in pediatric patients and total dose of the excipient, Captisol®, in the IM formulation.
General dosing instructions	See Table 1 in section 1.2
Dosing in patient subgroups (intrinsic and extrinsic factors)	N/A
Labeling	Within the PI for NDA 210864, Sections 2.3, 2.4 and 8.6 were updated to include the IV dosing recommendations in normal and renal impairment patients.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulations were used in both BE studies: 20-A98-AU (for IV) and 20-247-SA (for IM) studies. Please see Clinical Pharmacology review.

1.2. Dosing regimen

Table 1: Recommended IV Dosing Regimen for Adults and Pediatric Patients 2 Years and Older

Population	Initial Dosage	Infusion rate
For status epilepticus		
Adults (17 years of age and older)	15 mg PE/kg to 20 mg PE/kg	100 mg PE/min to 150mg PE/min, do not exceed a maximum rate of 150 mg PE/min
Non-emergent Loading Dosages		
Adult	10 mg PE/kg to 20 mg PE/kg	Not to exceed a maximum rate of 150 mg PE/min
Pediatric (2 years to less than 17 years of age)	10 mg PE/kg to 15 mg PE/kg	Not to exceed a maximum rate of 0.4 mg PE/kg/min
Maintenance Dosages		
Adult	Initial Maintenance Dosage: 4 mg PE/kg/day to 6 mg PE/kg/day in divided doses	Not to exceed a maximum rate of 0.4 mg PE/kg/min
Pediatric (2 years to less than 17 years of age)	Initial Maintenance Dosage: 2 mg PE/kg to 4 mg PE/kg (dose given 12 hours after the loading dose)	Not to exceed a maximum rate of 0.4 mg PE/kg/min
	Maintenance Dosage after Initial Maintenance Dosage: 4 mg PE/kg/day to 8 mg PE/kg/day in divided doses (continued every 12 hours after initial maintenance dose)	

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1. Pharmacokinetics of Sesquient

Refer to the Clinical Pharmacology review for pharmacokinetic information of IV and IM Sesquient compared to approved reference listed drug, Cerebyx®.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1. Pharmacokinetics of Captisol® in normal renal function patients

Captisol® is hydrophilic, not protein bound, and is excreted almost exclusively by glomerular filtration by the kidney. The properties of Captisol® suggest that it would accumulate in the presence of renal dysfunction and that it is dialyzable. Captisol® has been demonstrated to be safe and well tolerated in humans at a variety of dose levels. Pharmacokinetic studies completed in all species, including humans, have shown Captisol® is distributed in a volume similar to the species extracellular fluid (V_{ss} = 208 mL/kg) and is rapidly cleared unchanged (95% radioactivity) by the kidney (CL_r = 120 mL/min (i.e. 7.2 L/h, similar to GFR) with an elimination half-life ($t_{1/2}$) of 1.8 h in normal renal function patients.

3.2. Pharmacokinetics of Captisol® in moderate and severe renal impairment patients

In a recent study, adults were treated with a single dose of 300 mg IV delafloxacin/placebo containing 2400 mg Captisol®. Compared to normal renal function patients, Captisol® accumulation ($AUC_{0-\infty}$) was observed in moderate (~2-fold increase) and severe (~5-fold increase) renal impairment patients[1]. However total amount excreted unchanged in urine (Ae_{0-48}) was similar in all patients (normal and mild, moderate and severe renal impairment). The subjects (8 out of 33) experienced mild-to-moderate treatment emergent adverse events (TEAEs). This increase in AUC of Captisol® (~5-fold with severe renal impairment) warranted a dose adjustment from 300 mg every 12 hours to 200 mg every 12 hours delafloxacin in severe renal impairment patients with the dosing duration for IV delafloxacin as 5-14 days every 12 hours.

For Sesquient, each 1mg of fosphenytoin is delivered with 2mg of Captisol®. The labeled rate of delivery for status epilepticus in adults is up to 150mgPE/min of fosphenytoin. This results in Captisol® delivery of 300 mg/min during rapid loading. The total dose is up to 20 mg PE/kg. This results in a total Captisol® dose of 2800 mg during a loading dose of a 70 kg patient.
A second maintenance dose of fosphenytoin or phenytoin is recommended in the LD labeling and this maintenance dose is 3 mg PE/kg. If on day 1 a maximum loading (20 mg PE/kg) and maintenance dose (3 mg PE/kg) are administered to a 70 kg patient, this would result in a total day 1 dose of 1610 mg Sesquient and an associated dose of 3220 mg of Captisol®.

For the approved Carnexiv™, maximum 28,000 mg daily Captisol® can be administered. This amount is 10- and 8.7-folds higher than that of loading and loading + maintenance doses of Sesquient, respectively. Furthermore, although the label for approved Carnexiv™ states a maximum infusion rate of 233 mg/min for Captisol® (with a 30 minute infusion rate), clinical experience in 160 patients who received Carnexiv™ suggests a maximum Captisol® infusion rate

ranging from 525 mg/min to 1750 mg/min and a 35,000 mg total daily Captisol® dose in 4 patients was well tolerated. Refer to the Clinical review from 12/20/2019 in DARRTS for more information. These information support the maximum rate of Captisol® infusion (300 mg/min), the total day 1 loading and the exposure associated with short term Sesquient maintenance dosing. Thus, there is no dose adjustment needed for moderate and severe renal impairment patients and only close monitoring of serum creatinine for severe renal impairment patients is recommended. Also, refer to the Clinical review in by Dr. Steven Dinsmore (in DARRTS on 11/04/2020) for additional supportive safety information of Captisol®.

3.3. Pharmacokinetics of Captisol® in end-stage renal disease (ESRD) patients

A 2012 study evaluated multiple dosing of IV voriconazole (containing Captisol®) in ESRD patients (n=7) undergoing hemodialysis[2]. Patients received Captisol® doses of 192 mg/kg i.v. on Day 1 and 96 mg/kg/day IV for up to 5 days. Hemodialytic clearance of Captisol® increased from 2.6 off-dialysis to 48 mL/min during dialysis, elimination $t_{1/2}$ decreased from 79 h to 5 h and hemodialysis effectively removed Captisol® from the vascular space, resulting in plasma concentrations that approximate pre-dosing levels. Reported TEAEs were mild-to-moderate in severity.

3.4. Pharmacokinetics of Captisol® in pediatric patients

Parenteral products containing Captisol® are not indicated for use in patients under 2 years of age because of insufficient toxicological knowledge in the pediatric population. However, a small number of neonates treated with Captisol®-containing products at doses up to 336 mg/kg/day for 18 to 24 days did not show significant toxicity[3]. The EMA review also concluded that Captisol® doses as high as 250 mg/kg/day for 6 months in patients as young as 2 years of age are safe. In another study, the antifungal product, IV voriconazole was studied in pediatric patients 2-11 years of age[4]. The authors concluded that IV voriconazole was well tolerated in the pediatric patients with no patient discontinuing due to an adverse event attributable to the study drug. If IV voriconazole was administered as per the label (3 mg/kg/h), this would allow Captisol® to be delivered at a maximum infusion rate of 48 mg/kg/h (i.e. 0.8 mg/kg/min). Therefore, in line with the available clinical safety data in pediatric patients, the maximum infusion rate for Sesquient in pediatric patients is capped at 0.4 mg PE/kg/min (i.e. 0.8 mg Captisol®/kg/min). Also refer to the clinical review (by Dr. Steven Dinsmore) for a detailed interpretation of safety data of Captisol® in pediatric patients.

3.5. Pharmacokinetics of Captisol® after intramuscular (IM) Sesquient

No clinical data have been generated at this time on IM administration of Captisol® alone (without an active drug). The applicant's relative bioavailability study in healthy volunteers compared Sesquient IM with Cerebyx® IM (study 20-247-SA). The total dose of Captisol® in this study was 2000 mg (1000 mg PE) as a single IM dose. Refer to Clinical Pharmacology review for PK bridging findings. There were no unusual or unexpected adverse events related to the drug treatment. Although there are two FDA approved IM injection products (GEODON® and ABILIFY®) containing Captisol®, the total dose of Captisol® administered is 290 mg/day with

GEODON and 800 mg/day with ABILIFY® compared to the proposed total dose of 2800 mg in IM Sesquient formulation. Thus, due to lack of sufficient safety information for Captisol® with IM Sesquient, the Agency will not approve IM Sesquient and no labeling discussions can be made in this review cycle.

3.6. Post-marketing requirement (PMR)

None.

4. REFERENCES

1. Hoover RK et al., Clinical Pharmacokinetics of Sulfobutylether-β-Cyclodextrin in Patients With Varying Degrees of Renal Impairment. J Clin Pharmacol. 2018 Jun;58(6):814-822

2. Luke et al., Pharmacokinetics of sulfobutylether-β-cyclodextrin (SBECD) in subjects on hemodialysis, *Nephrology Dialysis Transplantation*, Volume 27, Issue 3, March 2012, Pages 1207–1212.

3. European Medicines Agency. Background review for cyclodextrins used as excipients: in the context of the revision of the guideline on 'excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1). 20 Nov 2014.

4. Walsh et al., Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. Antimicrob Agents Chemother. 2004 Jun;48(6):2166-72.

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA or BLA Number	210864
Submission Date	May 22, 2018
Submission Type	505(b)(2) NDA
Brand Name	SESQUIENT
Generic Name	Captisol-enabled fosphenytoin sodium injection
Dosage Form and Strength	Solution for Injection
Route of Administration	intravenous (IV) or intramuscular (IM)
Proposed Indication	Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery
Applicant	Sedor Pharmaceuticals, LLC
OCP Review Team	Hristina Dimova, Ph.D., Angela Men, M.D., Ph.D.

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1. EXECUTIVE SUMMARY

This is a 505(b)(2) New Drug Application (NDA) to support the marketing approval of SESQUIENT (Captisol®-Enabled Fosphenytoin Sodium Injection (CE-Fosphenytoin)). The sponsor is relying on the FDA's finding of safety and effectiveness for Cerebyx (NDA 020450), the listed drug (LD), and is seeking the same indication approved for Cerebyx: treatment of generalized tonic-clonic status epilepticus (SE) and for the prevention and treatment of seizures occurring during neurosurgery. CE-Fosphenytoin also can be substituted, as short-term use, for oral phenytoin. Fosphenytoin is a pro-drug that is rapidly converted to the active drug phenytoin in blood; therefore, fosphenytoin concentration in marketed fosphenytoin sodium injection products is expressed as milligrams of phenytoin equivalents (PE)/mL rather than as mg/mL. The fosphenytoin sodium formulation of 75 mg/mL is equivalent to 50 mg phenytoin sodium equivalents (PE)/mL following parenteral administration.

CE-Fosphenytoin is a drug product comprised of fosphenytoin sodium, USP, and a primary excipient sulfobutyl ether beta-cyclodextrin (i.e., Captisol®) (b) (4) This allows for room-temperature storage of the drug product at a more physiologic pH of 7(b)(4)–8.2. Fosphenytoin sodium injection products are labelled for storage under refrigerated conditions (Cerebyx Prescribing Information, Pfizer Inc, 2017).

The clinical program included two pivotal bioequivalence (BE) studies to compare CE-Fosphenytoin to Cerebyx: Study 20-A98-AU (CE-Fosphenytoin Versus Cerebyx® After IV Administration) and Study 20-247-SA (CE-Fosphenytoin Versus Cerebyx® After IM Administration). Bioequivalence (in terms of plasma phenytoin levels) was demonstrated in both studies, establishing clinical bridge for CE-Fosphenytoin versus Cerebyx.

A consult was sent to the Office of Scientific Inspections and Surveillance (OSIS) requesting clinical and bioanalytical site inspections for BE studies 20-A98-AU and 20-247-SA. OSIS concluded that the data are acceptable based on the records of recent inspections of these clinical and bioanalytical sites.

1.1 Recommendations

The office of Clinical Pharmacology (OCP) has reviewed the information contained in NDA 210864 and finds it acceptable from an OCP perspective. The approvability of Sesquient will be deferred to the clinical review team. Key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The demonstration of bioequivalence for CE-Fosphenytoin versus Cerebyx has been determined on the basis of bioequivalent plasma phenytoin levels; therefore, pharmacokinetic bridge for CE-Fosphenytoin versus Cerebyx has been established.
Safety Issues	There is insufficient safety data to support the infusion rate and total dose of the excipient Captisol.

General dosing instructions	N/A
Dosing in patient subgroups (intrinsic and extrinsic factors)	N/A
Labeling	Labeling recommendations cannot be made at this time.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the pivotal BE studies.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Fosphenytoin is a pro-drug that undergoes rapid presystemic hydrolysis by esterases and is converted to the active moiety phenytoin. The precise mechanism by which phenytoin exerts its therapeutic effect has not been established but is thought to involve the voltage-dependent blockade of membrane sodium channels resulting in a reduction in sustained high-frequency neuronal discharges.

When fosphenytoin sodium injection is administered by IV infusion, maximum plasma fosphenytoin concentrations are achieved at the end of the infusion.

Plasma fosphenytoin concentrations following IM administration are lower but more sustained than those following IV administration due to the time required for absorption of fosphenytoin from the injection site. Fosphenytoin is completely converted to phenytoin and plasma total phenytoin concentrations peak is occurred in approximately 3 hours (Cerebyx PI 2017).

CE-Fosphenytoin bioequivalence to fosphenytoin sodium injection (based on bioequivalent plasma phenytoin levels) was demonstrated as part of this NDA application. Additionally, phenytoin exposure following fosphenytoin sodium injection has been well established (Cerebyx PI and literature). Following parenteral administration, fosphenytoin is completely converted to phenytoin by blood and tissue phosphatases with a half-life that ranges from 7-15 mins (Fischer 2003). For every mmol of fosphenytoin administered, one mmol of phenytoin is produced. The anticonvulsant effects of fosphenytoin are attributable to the pharmacologically active metabolite phenytoin.

2.1.1 Pharmacokinetic Comparison between SESQUIENT and Cerebyx

The demonstration of bioequivalence for CE-Fosphenytoin versus the LD Cerebyx has been determined on the basis of bioequivalent plasma phenytoin levels in two bioequivalence trials (i.e., Studies 20-247-SA and 20-A98-AU).

IV BE Study 20-A98-AU: The geometric mean ratio (GMR) and 90% confidence intervals (CI) for ln(C_{max}) and ln(AUC_{last}) between Test (CE-Fosphenytoin) and Ref (Cerebyx) were within the accepted 80% to 125% limits for total and free levels of phenytoin in plasma and plasma ultrafiltrate respectively.

IM BE Study 20-247-SA: The geometric mean ratio (GMR) and 90% CI for ln(C_{max}) and ln(AUC_{last}) were within the accepted 80% to 125% limits for total levels of phenytoin in plasma.

Note: Blood samples were collected up to 48 hours, not long enough for assessing terminal slope (and AUC_{inf}) after the administration of the study drugs (Ref and Test). Refer to Sect 3.3.1 for additional comments.

Plasma samples were analyzed for free and total phenytoin using validated LC-MS/MS methods. Details of the method validation and sample analysis procedures are provided in the Appendix 4.1.1.

The formulation used in the two bioequivalence trials is identical to the formulation in the primary stability batches for this application and in the planned registration batches.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The sponsor proposed no greater than 150 mg PE/min in adults and 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower) in pediatric patients for status epilepticus followed by maintenance dose. Non-emergent Loading and Maintenance Dosing: no greater than 150 mg PE/min in adults. For loading doses in pediatric patients, the rate should not exceed 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower). For maintenance doses in pediatric patients, the rate should not exceed 1 to 2 mg PE/kg/min (or 100 mg PE/min, whichever is slower).

There is insufficient safety data to support the administration rate and total dose of the excipient Captisol. This product cannot be approved at this time (see Clinical Review for details). Dosing recommendations will not be provided.

2.2.2 Therapeutic individualization

N/A

2.3 **Post-Marketing Commitment**

None is identified.

2.4 Summary of Labeling Recommendations

No labeling recommendation is provided at this stage.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

This is a 505(b)(2) NDA to support the approval of SESQUIENT (CE-Fosphenytoin). The sponsor is relying on the FDA's finding of safety and effectiveness for Cerebyx (NDA 020450) as the LD.

CE-Fosphenytoin bioequivalence to fosphenytoin sodium injection was demonstrated as part of this NDA application. The selection of the doses used in these studies was based on the Division's recommendations at the Pre-IND meeting with the previous sponsor CyDex Pharmaceuticals, Inc.

Additionally, at the preNDA Meeting (2008), the Division stated that the NDA submission should include a discussion of the potential toxicity of the excipient (b) (4) sulfobutyl ether beta-cyclodextrin (Captisol®) in patients based on overall daily exposure and rate of administration. This discussion should compare estimated exposures of Captisol in the proposed Captisol-enabled fosphenytoin product given intravenously and intramuscularly with that of Captisol in currently FDA-approved products (e.g. V-FEND) and any other products for which the sponsor may have Captisol data. One special area of interest is that of renal toxicity.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Note: This section is based in part on the nonclinical and clinical information described within the previously submitted marketing applications for phenytoin sodium and fosphenytoin sodium injection.

Pharmacology	
Mechanism of Action	The precise mechanism by which phenytoin exerts its therapeutic effect has not been established but is thought to involve the voltage-dependent blockade of membrane sodium channels resulting in a reduction in sustained high-frequency neuronal discharges (Cerebyx PI 2017).
General Information	
Bioanalysis	Plasma samples were analyzed for free and total phenytoin using validated LC-MS/MS methods. The methods were validated over the range 50.0 to 35,000 ng/mL for total phenytoin, and over the range of 10.0 to 4000 ng/mL for free phenytoin based on the analysis of 0.2 mL of human K2-EDTA plasma or plasma ultrafiltrate.
Healthy Volunteers vs Patients	NA The BE studies were conducted in healthy subjects.
ADME	

Absorption	Following parenteral administration, fosphenytoin is completely converted to the phenytoin by blood and tissue phosphatases with a half-life that ranges from 7-15 mins (Fischer 2003). For every mmol of fosphenytoin administered, one mmol of phenytoin is produced. When fosphenytoin sodium is administered by IV infusion, maximum plasma fosphenytoin concentrations are achieved at the end of the infusion. Plasma fosphenytoin concentrations following IM administration are lower but more sustained than those following IV administration. Fosphenytoin is completely bioavailable following IM administration and plasma total phenytoin concentrations peak in approximately 3 hours (Cerebyx PI 2017).
Distribution	Fosphenytoin is extensively bound (95% to 99%) to human plasma proteins, primarily albumin. Binding to plasma proteins is saturable with the result that the percent bound decreases as total fosphenytoin concentrations increase. Fosphenytoin displaces phenytoin from protein binding sites. The volume of distribution of fosphenytoin increases with the dose and rate of administration, and ranges from 4.3 to 10.8 liters.
Metabolism	Fosphenytoin is a pro-drug that undergoes rapid presystemic hydrolysis by esterases and is converted to the active moiety phenytoin. For every mmol of fosphenytoin administered, one mmol of phenytoin is produced. The pharmacokinetics of fosphenytoin following IV administration of Cerebyx, however, are complex. Studies have empirically determined an infusion rate for Cerebyx that gives a rate and extent of phenytoin systemic availability similar to that of a 50 mg/min phenytoin sodium infusion. A dose of 15 to 20 mg PE/kg of Cerebyx infused at 100 to 150 mg PE/min yields plasma free phenytoin concentrations over time that approximate those achieved when an equivalent dose of phenytoin sodium (e.g., parenteral DILANTIN®) is administered at 50 mg/min. Phenytoin derived from administration of CEREBYX is extensively metabolized in the liver by the cytochrome P450 enzymes CYP2C9 and CYP2C19.
Elimination	The conversion half-life of fosphenytoin to phenytoin is approximately 15 minutes. Mean total phenytoin half-life values (12.0 to 28.9 hr) following Cerebyx administration are similar to those after equal doses of parenteral Dilantin and tend to be greater at higher plasma phenytoin concentrations.

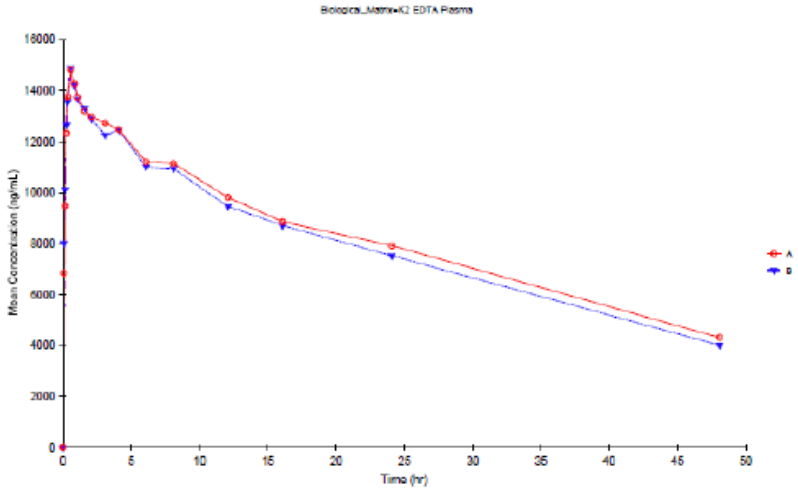
3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

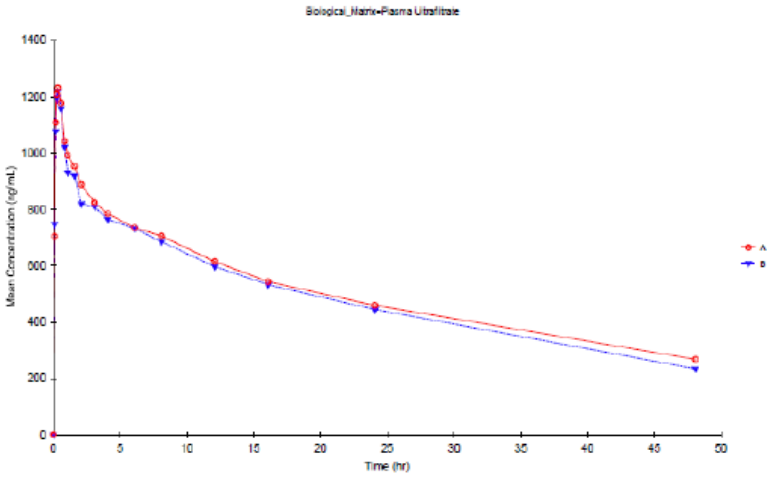
No efficacy studies were conducted for this NDA. The sponsor has provided an adequate bridging information to the reference drug, Cerebyx (NDA 020450) to support the efficacy of its CE-Fosphenytoin injection product. Two BE studies (i.e., Study 20-247-SA for intramuscular injection and Study 20-A98-AU for intravenous infusion) were conducted to compare CE-Fosphenytoin to Cerebyx; the design and the results from these two studies are summarized below.

Study No.	Study Design and Objective	Enrolled Population	Study Drug, Dose, and Frequency	Number of Completed Subjects	Treatment periods
20-A98-AU	A Double-Blind, Randomized, 2-Treatment, 2-Period Crossover Study Comparing the Pharmacokinetics of Captisol-Enabled Fosphenytoin Sodium with Cerebyx after IV Administration	Healthy volunteers; 19 M/19 F; 23-53 yr	**Treatment A**: Test Formulation CE-fosphenytoin (Lot # 2108-102) (50 mg PE/mL) Dose = 1 × 10 mg PE/kg intravenous infusion at rate of 150 mg PE per minute 14 day washout period **Treatment B**: Reference product Cerebyx (50 mg PE/mL) Dose = 1 × 10 mg PE/kg IV infusion at rate of 150 mg PE per minute	34	Subjects were randomized to 1 of 2 treatment sequences: Sequence 1 (CE-fosphenytoin and Cerebyx) or Sequence 2 (Cerebyx and CE-fosphenytoin), with the periods separated by a 14-day washout period
20-247-SA	A Double-Blind, Randomized, 2-Treatment, 2-Period Crossover Study Comparing the Pharmacokinetics of Captisol-Enabled Fosphenytoin Sodium with Cerebyx Administered Via IM Injection in Normal Healthy Volunteers	Healthy volunteers; 26 M/26 F; 18-55 yr	**Treatment A**: Test Formulation CE-fosphenytoin (Lot #2108-102) 1000 mg PE (4 x 5 mL IM injections) 14 day washout period **Treatment B**: Reference product Cerebyx 1000 mg PE (4 x 5 mL IM injections)	50	Subjects were randomized to 1 of 2 treatment sequences: Sequence 1 (CE-fosphenytoin and Cerebyx) or Sequence 2 (Cerebyx and CE-fosphenytoin), with the periods separated by a 14-day washout period

Study 20-A98-AU Captisol-Enabled® Fosphenytoin Sodium Versus Cerebyx® After IV Administration: Mean Phenytoin Concentration-Time Profiles in K2-EDTA Plasma after Administration of the Test Formulation (Treatment A) and the Reference Product (Treatment B)



Study 20-A98-AU: Mean Phenytoin Concentration-Time Profiles in Plasma Ultrafiltrate after Administration of the Test Formulation (Treatment A) and the Reference Product (Treatment B)



Study 20-A98-AU: Pharmacokinetic Parameters of Total Phenytoin in K2-EDTA Plasma

Parameter	Treatment A: Test Formulation				Treatment B: Reference Product (Cerebyx)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	34	1.26	1.55	122.41	34	0.78	0.61	78.17
C_{max} (ng/mL)	34	15900	2650	16.68	34	15900	2310	14.57
AUC_{last} (hr*ng/mL)	34	391500	87700	22.40	34	370200	85230	23.02
λ_z (hr^{-1})	34	0.0269	0.0111	41.38	34	0.0283	0.0119	42.15
$T_{1/2}$ (hr)	34	32.28	20.00	61.96	34	28.97	11.95	41.25
T_{last} (hr)	34	48.08	0.00	0.00	34	46.68	5.73	12.28
C_{last} (ng/mL)	34	4310	2130	49.30	34	4180	1900	45.56

AUC_{inf} values not reported (extrapolated portion of AUC >20%)

Study 20-A98-AU: Pharmacokinetic Parameters of Free Phenytoin in K2-EDTA Plasma

Parameter	Treatment A: Test Formulation				Treatment B: Reference Product (Cerebyx)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	34	0.45	0.38	84.30	34	0.38	0.19	50.11
C_{max} (ng/mL)	34	1420	370	25.96	34	1350	314	23.22
AUC_{last} (hr*ng/mL)	34	24410	3981	16.31	34	22970	4050	17.63
λ_z (hr^{-1})	33	0.0283	0.0114	40.30	34	0.0291	0.0105	36.06
$T_{1/2}$ (hr)	33	29.72	14.85	49.98	34	27.27	10.81	39.64
T_{last} (hr)	34	48.08	0.00	0.00	34	46.68	5.73	12.28
C_{last} (ng/mL)	34	268	168	62.76	34	246	103	42.01

AUC_{inf} values not reported (extrapolated portion of AUC >20%)

Study 20-A98-AU: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Total Phenytoin in K2-EDTA Plasma

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA CV%
	Test	Ref	(Test/Ref)	Lower	Upper		
$ln(C_{max})$	15566	15664	99.4	96.1	102.8	1.0000	8.18
$ln(AUC_{last})$	381883	361907	105.6	101.2	110.1	1.0000	10.20
$ln(AUC_{inf})$	ND	ND	ND	ND	ND	ND	ND

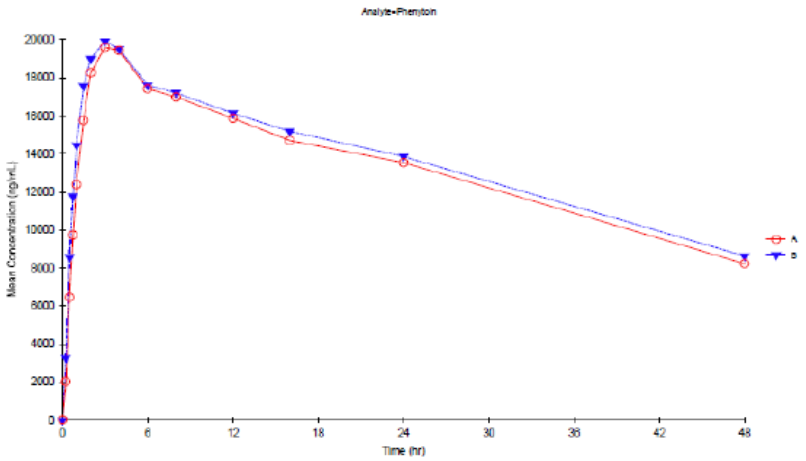
[a] Geometric Mean for the Test Formulation (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
ND: Not Determined (Extrapolated AUC_{inf} >20%)

Study 20-A98-AU: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Free Phenytoin in Plasma Ultrafiltrate

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA CV%
	Test	Ref	(Test/Ref)	Lower	Upper		
$ln(C_{max})$	1380	1312	105.1	100.0	110.5	1.0000	12.13
$ln(AUC_{last})$	24120	22655	106.5	101.9	111.3	1.0000	10.73
$ln(AUC_{inf})$	ND	ND	ND	ND	ND	ND	ND

[a] Geometric Mean for the Test Formulation (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
ND: Not Determined (Extrapolated AUC_{inf} >20%)

Study 20-247-SA Captisol-Enabled® Fosphenytoin Sodium Versus Cerebyx® After IM Administration: Mean Phenytoin Concentration-Time Profiles in Plasma after Intramuscular Administration of the Test Formulation (Treatment A) and the Reference Product (Treatment B)



Study 20-247-SA: Pharmacokinetic Parameters of Phenytoin Following Intramuscular Administration of Test Formulation and the Reference Product

Parameter	Treatment A: Test Formulation				Treatment B: Reference Product (Cerebyx)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	50	3.24	0.84	25.96	50	3.23	1.32	40.97
C_{max} (ng/mL)	50	20100	4420	21.98	50	20400	4660	22.78
AUC_{last} (hr*ng/mL)	50	629700	170700	27.11	50	646100	192800	29.84
λ_z (hr^{-1})	48	0.0204	0.0073	35.64	49	0.0195	0.0076	39.13
$T_{1/2}$ (hr)	48	42.83	32.70	76.33	49	47.31	52.25	110.44
T_{last} (hr)	50	47.70	3.47	7.28	50	47.41	5.05	10.64
C_{last} (ng/mL)	50	8260	3500	42.39	50	8760	3840	43.88

AUC_{inf} values not reported (extrapolated portion of AUC >20%)

Study 20-247-SA: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phenytoin in Plasma

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA CV%
	Test	Ref	(Test/Ref)	Lower	Upper		
ln(C_{max})	19652	19942	98.6	97.1	100.1	1.0000	4.53
ln(AUC_{last})	608220	620379	98.0	94.4	101.8	1.0000	11.53
ln(AUC_{inf})	ND	ND	ND	ND	ND	ND	ND

[a] Geometric Mean for the Test Formulation (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
ND: Not Determined (Extrapolated AUC_{inf} >20%)

Reviewer's Comments: Blood samples were collected up to 48 hours, not long enough for assessing terminal slope (and AUC_{inf}) after the administration of the study drugs (Ref and Test). However, per the Bioavailability and Bioequivalence Guidance (2014), for drugs with a long half-life, truncated AUC can be used (Section VII.D, Long-Half-Life Drugs). In addition, in both studies (20-A98-AU and 20-247-SA), the individual phenytoin concentration-time profiles after administration of the Test were similar to these after administration of Ref. The terminal slopes after Test and Ref were parallel (or overlapping) for all subjects in the studies. Therefore, there is no evidence that truncating AUC to 48h could affect the BE conclusions (e.g. AUC_{inf} not available).

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Based on bioequivalence of fosphenytoin/phenytoin exposures between Cerebyx and SESQUIENT (refer to Sect 3.3.1), the proposed dosing regimen would have been acceptable.

However, the potential toxicity of the excipien [redacted] (b) (4) Captisol® in SESQUIENT formulation should be considered, refer to Sect 3.1 Overview of the Product and Regulatory Background.

Ingredients	Concentration	Composition		Function
		(b) (4)	Vial 10 mL	
Active Substances(s)				
Fosphenytoin Sodium	75mg/mL[1]		(b) (4)	Active ingredient
Excipients				
Captisol	100 mg/mL			(b) (4)

*2ml fill volume

[1]equivalent to 50 mg phenytoin sodium

A primary use of fosphenytoin is treatment of status epilepticus. Fosphenytoin may also be used for short term phenytoin maintenance therapy when oral phenytoin administration is not possible. An adult loading dose of fosphenytoin is 15 to 20 mg PE/kg at a rate of 100 to 150 mg/min while a pediatric loading dose is 15 to 20 mg PE/kg at a rate of 2 mg PE/kg/min or 150 mg PE/ min, whichever is slower. An adult loading dose for a 60 kg individual would deliver a total Captisol dose of 2400 mg at a rate of 300 mg/min.

Captisol concentrations were not measured in the BE studies in the current NDA submission. Instead, the sponsor has provided a table with the total daily Captisol dose and rate of IV infusion for SESQUIENT relative to these in other FDA approved Captisol-containing products. Later in the review cycle (Dec.14, 2018), the sponsor clarified that that the only listed drug on which they are relying for approval of their application is Cerebyx; information related to any listed drug other than Cerebyx that was included in their original application, may not be considered. The sponsor also clarified that they are relying on published literature and on Drug Master File (DMF) # 14364 (CyDex Pharmaceuticals, Inc.) for the clinical safety of the excipient Captisol. However, it was determined that the information in DMF # 14364 and published literature does not contain sufficiently comprehensive safety data, frequency of exposure, total exposure or maximum rate of exposure to support for the 2400mg total dose of Captisol or maximum infusion rate of 300mg/min of Captisol that are delivered for the indication of status epilepticus or the pediatric age (please refer to NDA 210864 Clinical Review, Section 7.5.1).

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Due to the insufficient safety data to support the infusion rate and total dose of the excipient Captisol, labeling recommendations cannot be made at this time.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No food effect is expected as Sesquient is for IV or IM administration only.

No drug interaction studies were conducted with Sesquient, however there is no reason to expect any new (relative to Cerebyx) drug interactions for this product.

4. APPENDICES

4.1: Summary of Bioanalytical Method Validation and Performance

4.1.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Plasma samples were analyzed for free and total phenytoin using validated LC-MS/MS methods. The methods were validated according to the FDA Guidance for Industry on Bioanalytical Method Validation (2013) over the range 50.0 to 35,000 ng/mL for total phenytoin, and over the range of 10.0 to 4000 ng/mL for free phenytoin based on the analysis of 0.2 mL of human K2-EDTA plasma or plasma ultrafiltrate.

Bench top stability was determined to be at least 24 hours and QC samples were stable following 5 freeze/thaw cycles. Plasma phenytoin samples were stable on frozen storage for at least 130 days at -20^{0}C and -70^{0}C.

No interfering peaks were detected in six lots of human plasma and in the presence of multiple over-the-counter drugs including acetaminophen, acetylsalicylic acid, brompheniramine, caffeine, chlorpheniramine, cimetidine, dextromethorphan, diphenhydramine, famotidine, ibuprofen, ketoprofen, loratadine, naproxen, omeprazole, pseudoephedrine, ranitidine, salicylic acid, and triprolidine.

Summary of the methods validations and sample analysis procedures are provided below.

Summary of Bioanalytical Method Validation DCN 1002722

Analytical Method used during validation	Validation Report Number: DCN: 1002722 Determination of Phenytoin in Human K2-EDTA Plasma by LC-MS-MS
Short description of the method	Human plasma containing phenytoin and the IS phenytoin-D10, was extracted by liquid-liquid extraction, evaporated to dryness and reconstituted in mobile phase. An aliquot of the extract was injected onto a Sciex API 4000 LC-MS-MS. The peak area of the m/z 251→102 phenytoin product ion was measured against the peak area of the m/z 261→106 phenytoin-D10 internal standard product ion.
Biological matrix	Human Plasma (K2EDTA)
Analyte	Phenytoin
Internal standard (IS)	phenytoin-D10
Calibration concentrations (Units)	50 – 35,000 ng/mL
Linearity	R2: 0.9963
QC levels:	150, 7000 and 28,000 ng/mL
Average recovery of drug (%)	87.5
Average recovery of IS (%)	96.4
Dilution integrity	100,000 ng/mL diluted 10 times for phenytoin
QC Interday accuracy (%Nominal)	-0.4 – 7.3
QC Interday precision (%CV)	≤7.8
QC Intraday accuracy (%Nominal)	-6.1 – 14.0
QC Intraday precision (%CV)	≤3.3

Bench top (Short term) stability in biological matrix at room temperature.	24 hours at RT
Long term frozen stability	At least 130 days at -20^{0}C and -70^{0}C
Processed sample stability	5 freeze/thaw cycles
Selectivity	No interfering peaks noted in blank plasma samples
Interference from common drugs	No impact on quantitation

Summary of Bioanalytical Method Validation DCN 1002421

Analytical Method used during validation	Validation Report Number: DCN: 1002421 Determination of Phenytoin in Human K2-EDTA Plasma Ultrafiltrate by LC-MS-MS
Short description of the method	Human plasma ultrafiltrate containing phenytoin and the IS phenytoin-D10, was extracted by liquid-liquid extraction, evaporated to dryness and reconstituted in mobile phase. An aliquot of the extract was injected onto a Sciex 4000 LC-MS-MS. The peak area of the m/z 251→102 phenytoin product ion was measured against the peak area of the m/z 261→106 phenytoin-D10 internal standard product ion.
Biological matrix	Human plasma ultrafiltrate
Analyte	Phenytoin
Internal standard (IS)	phenytoin-D10
Calibration concentrations (Units)	10 – 4000 ng/mL
Linearity	R2 ≥ 0.9990
Average recovery of drug (%)	107 - 126
Average recovery of IS (%)	122
QC levels	30, 750, 3000 ng/mL
QC Interday accuracy (%Nominal)	5.3 – 11.9
QC Interday precision (%CV)	≤ 4.7
QC Intraday accuracy (%Nominal)	2.3 – 14.3
QC Intraday precision (%CV)	≤ 5.0
Bench top (Short term) stability in biological matrix at room temperature.	At least 23 hours
Long term frozen stability	At least 130 days at -20^{0}C and -70^{0}C
Processed sample stability	5 freeze/thaw cycles
Selectivity	No interfering peaks noted in blank plasma samples

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/s/

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03/15/2019 05:35:59 PM

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