CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210864Orig1s000

SUMMARY REVIEW

Summary Review

Date	November 2, 2020
From	Philip H. Sheridan, MD Nick Kozauer, MD
Subject	Summary Review for Class 2 NDA Resubmission
NDA/BLA # and Supplement#	210864 Suppl 029
Applicant	Sedor Pharmaceuticals, LLC
Date of Submission	May 8, 2020
PDUFA Goal Date	November 8, 2020
Proprietary Name	Sesquient
Established or Proper Name	Fosphenytoin sodium injection (with betadex sulfobutyl ether sodium)
Dosage Forms/Strengths	Solution for intravenous administration; (b) (4) 10mL vial, both at a concentration of 50 mg phenytoin equivalents (PE)/mL
Dosing	<u>For status epilepticus:</u> *Adult* loading dose is 15 to 20 mg PE/kg at a rate of 100 to 150 mg PE/min. <u>For non-emergent loading and maintenance dosing:</u> *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	For adults: treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery. For adults and children age 2 years and older: nonemergent loading and short-term substitution for oral phenytoin maintenance when oral phenytoin administration is not possible.
Recommendation on Regulatory Action	Approval

1. Introduction and Regulatory History

This is a Class 2 resubmission of NDA 210864 following Complete Responses on March 22, 2019, and December 20, 2019, due to product quality, clinical safety, and patent certification issues.

In this 505(b)(2) submission for Sesquient (fosphenytoin sodium injection with betadex sulfobutyl ether sodium), the applicant again relies on the Agency's prior finding of safety and effectiveness for Cerebyx (NDA 020250), as a listed drug (LD), and seeks the same indications approved for Cerebyx: treatment of generalized tonic-clonic status epilepticus, prevention and treatment of seizures occurring during neurosurgery, and short-term substitution for oral phenytoin maintenance when oral phenytoin administration is not possible.

Original NDA Submission (May 22, 2018)

In the original submission of this NDA on May 22, 2018, the applicant submitted chemistry, manufacturing, and control (CMC) information, the results from two pivotal bioequivalence (BE) studies which compared Sesquient to Cerebyx (Study 20-A98-AU after IV administration and Study 20-247-SA after IM administration) as well as some nonclinical and clinical safety information for the primary excipient Captisol (betadex sulfobutyl ether sodium) to support approval.

The Office of Clinical Pharmacology (OCP) reviewers found the data from the two pivotal BE studies to be adequate to support approval. BE (in terms of plasma phenytoin levels) was demonstrated in both studies, establishing a clinical bridge between Sesquient and Cerebyx.

The Office of Product Quality (OPQ) review team recommended that the Agency issue a Complete Response letter because this submission did not include adequate information to ensure that the applicant could consistently manufacture a product that was suitable for the proposed clinical indications.

The nonclinical reviewers concluded that the nonclinical data in the first NDA submission and available in the Captisol Drug Master File (DMF (# 14364) (for which a letter of authorization was submitted), although having been found to be adequate to support the initiation of adult clinical studies of CE-fosphenytoin, could not support approval without adequate clinical safety data.

The clinical review team concluded that there was a lack of adequate clinical safety data to support the safety of the excipient (b) (4) Captisol in the Sesquient formulation. The applicant relied only on the clinical safety data from the BE studies (A98 and 247) provided in the application, the published literature provided in the application, and the Captisol DMF (# 14364) to support the clinical safety of the excipient Captisol. These data either did not contain sufficiently detailed safety data or did not adequately address the dosing frequency, total exposure, and/or a maximum rate of exposure to support the safety of Sesquient for the proposed indication of status epilepticus in any age group.

Given the CMC deficiencies identified and the inadequate clinical safety data with respect to Captisol for the status epilepticus indication, a Complete Response (CR) letter for the first NDA submission was issued on March 22, 2019.

First Class 2 NDA resubmission (June 28, 2019)

In its review of the first Class 2 NDA resubmission, the CMC review team again concluded that the (b) (4) particulate material identified in Sesquient was a safety hazard.

A teleconference was held with the applicant on November 7, 2019, during which it was determined that the source of the particulates remained unidentified and that a solution to eliminating this impurity was not yet available. The applicant submitted a quality information amendment on December 6, 2019, which provided additional study results from (b) (4) regarding particles in the drug product. In this amendment, the applicant concluded that the initial particulate information, obtained in association with the (b) (4) testing, was erroneous and not representative of the drug product due to the testing environment conditions. However, the CMC reviewers determined that there was not sufficient information (e.g., documentation of environmental conditions when the (b) (4) testing was performed) to confirm that the initial results from the (b) (4) study were erroneous. Thus, the CMC reviewers concluded that the (b) (4) study report did not conclusively support the applicant's contention that the root cause for the particulates observed and characterized by (b) (4) in Sesquient is laboratory error, and that the (b) (4) results could not be disregarded. Therefore, the OPQ team again recommended issuance of a Complete Response Letter.

The clinical review team found that the applicant, now also relying on Carnexiv as a LD with respect to the safety of Captisol (NDA 206030), had provided additional support for the use of Captisol at the rapid rate of infusion and the total dose required for the Sesquient indication of status epilepticus for adults but not for children.

In addition, there were several deficiencies regarding the need for a required update of FDA form 356S (to reflect reliance on only Cerebyx and Carnexiv NDAs), and documentation of notice of Paragraph IV certification notice to Ligand Pharmaceuticals, owner of Cydex (a Ligand Company) (Cydex is the owner of Captisol and the Cydex Drug Master File [DMF] 14364). In addition, clear documentation of a receipt from Lundbeck Pharmaceuticals of the Paragraph IV certification that had been previously transmitted to Lundbeck Pharmaceuticals was needed.

Given the persistent CMC deficiencies identified and the patent-related issues, a Complete Response letter for the first Class 2 NDA resubmission was issued on December 20, 2019.

Current Submission (Second Class 2 NDA Resubmission), May 8, 2020

The current submission is the applicant's second Class 2 NDA Resubmission (third review cycle submission). The product quality, clinical pharmacology, and clinical reviews are summarized below in Sections 2, 3, and 4 of this summary review.

2. Product Quality

The technical lead for the product quality review team was Dr. Martha Heimann, and the reviewers were Dr. Andrei Ponta (drug product/labeling), Dr, Peter Krommenhoek (manufacturing), and Dr. Kelly Ballard (regulatory business).

As discussed in Section 1 of this summary review, in the CR letter of December 20, 2019, the OPQ review team asked the applicant to characterize the particles observed in the drug product and identify the root cause of their presence (e.g., container closure system, testing method/conditions, manufacturing equipment), to provide a risk mitigation and control plan to mitigate the presence of particulates in Sesquient, and to provide data demonstrating that the actions taken will prevent reoccurrence of particles in Sesquient.

The OPQ review team notes that the applicant has now provided a root cause analysis investigating the particulate testing and results from (b) (4). This investigation considered whether procedural differences between the two labs (e.g., environmental conditions, personnel, equipment, test samples, and methods) could have caused the differences in results. As a result of the investigation the applicant documented several differences between the sites. The most significant differences relate to environmental conditions, types of testing performed, and sampling procedures. Based on the findings of the root cause investigation and the more rigorous testing procedures at (b) (4), the OPQ review team finds that it is reasonable to conclude, as argued by the applicant, that environmental cross contamination may have occurred during testing at (b) (4). Thus, the OPQ team accepts the data obtained from (b) (4) as indicating that the drug product does not contain any (b) (4) particle contaminants.

In addition, the OPQ review team concludes that the applicant's risk mitigation strategy to reduce particulates during the manufacture of the drug product is adequate and that all facilities involved in manufacture or testing of Sesquient are currently acceptable.

The OPQ recommends approval of this Class 2 NDA Resubmission.

3. Clinical Pharmacology

The clinical pharmacology review was written by Dr. Adarsh Gandhi (reviewer) and Dr. Angela Men (supervisory reviewer).

As discussed in Section 1 of this summary review, the clinical pharmacology review team had previously reviewed two Phase 1 relative BE studies [Study 20-A98-AU (Sesquient vs. Cerebyx after intravenous (IV) administration) and Study 20-247-SA (Sesquient vs. Cerebyx after intramuscular (IM) administration] and had concluded that Sesquient and Cerebyx are bioequivalent after both IV and IM dosing in healthy volunteers.

This current clinical pharmacology review addresses the remaining issue of Captisol in renal impairment patients. Based on the clinical information in DMF 14364 and from the LD, Carnexiv (NDA 206030), the clinical pharmacology review team concludes 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. This information will be added to Section 8.6 of the prescribing information for Sesquient.

The clinical pharmacology review has determined that a dosing recommendation for IM Sesquient cannot be made at this time as the safety of the total Captisol dose at the proposed IM dosing has not been established.

The Office of Clinical Pharmacology recommends approval of this Class 2 NDA Resubmission.

4. Clinical

The clinical review was written by Dr. Steven Dinsmore (reviewer).

During the first review cycle, Dr. Dinsmore noted that the applicant was not able to support the clinical safety of the Captisol component of Sesquient for status epilepticus in any age-group.

In his review of the first Type 2 NDA resubmission, Dr. Dinsmore, found that the applicant had provided additional support from reliance on Carnexiv (NDA 020450) for the use of Captisol at the rapid rate of infusion and the total dose required for the Sesquient indication of status epilepticus for adults but not for children.

In his review of the current (second) Type 2 NDA resubmission, Dr. Dinsmore indicates that the patent-related issues identified in the CR letter of December 20, 2019, have been adequately addressed.

Dr. Dinsmore notes that there are three publications in the Captisol DMF (DMF 14364), relied upon by the applicant, that characterize the safety of the Captisol-containing intravenous antifungal drug voriconazole when used in the pediatric population age 2 years and older. In his clinical review, Dr. Dinsmore examines the data from these publications in detail. Dr. Dinsmore concludes that the total dose and rate of administration of Captisol described in these publications support the proposed non-urgent pediatric dosing down to 2 years of age. He notes that a total of 109 patients are captured in these studies with an age range that adequately represents the age range of the proposed non-urgent pediatric indications for Sesquient. He does not identify any safety signals that differ from the known safety profile of voriconazole or those expected in the study populations. Dr. Dinsmore concludes that these publications support the pediatric safety of Captisol for non-urgent loading dose or replacement phenytoin therapy indication of Sesquient at a maximum delivery rate of 0.4mgPE/kg/min.

Dr. Dinsmore further notes, however, there are no data to support the safety of faster infusion rates required for the pediatric indications of status epilepticus or treatment of seizures during neurosurgery.

Dr. Dinsmore discusses the applicant's suggestion that the BE study (Study 20-247-3A) provides safety support for the IM use of Sesquient with its Captisol content. He notes that Study 20-247-3A was a single dose study; therefore, safety is only supported for a single IM dose in adults in contrast to the LD labeling which indicates that Cerebyx could be administered IM as a short-term substitute for oral phenytoin (i.e., allowing for multiple doses). He further notes that there are no data to support the safety of IM administration in pediatric patients. Thus, Dr. Dinsmore concludes that there is insufficient safety data to approve the IM administration of Sesquient in any age group.

Dr. Dinsmore recommends the approval of this Class 2 NDA resubmission for Sesquient, administered IV but not IM, for the proposed indications for adult patients and for the nonurgent loading and short-term maintenance indications for pediatric patients age 2 years and older.

5. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

6. Postmarketing Recommendations

There are no postmarketing requirements or commitments.

7. Conclusion

This Class 2 NDA resubmission will be approved.

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/s/

PHILIP H SHERIDAN
11/04/2020 07:30:15 PM

NICHOLAS A KOZAUER
11/05/2020 04:48:15 PM

Summary Memorandum for Class 2 NDA Resubmission

Date	December 20, 2019
From	Philip H. Sheridan, MD Nick Kozauer, MD
Subject	Summary Memorandum for Class 2 NDA Resubmission
NDA#	NDA 210864
Applicant	Sedor Pharmaceuticals, LLC
Date of Submission	June 28, 2019
PDUFA Goal Date	December 28, 2019
Proprietary/ Established (USAN) Name	Sesquient (Captisol-enabled fosphenytoin sodium Injection)
Dosage forms / Strength	Solution for intravenous (IV) or intramuscular (IM); (b) (4) and 10ml vial and both at a concentration of 50 mg phenytoin equivalents (PE)/mL
Proposed Indication(s)	Treatment of generalized tonic-clonic status epilepticus, prevention and treatment of seizures occurring during neurosurgery, short-term substitution for oral phenytoin maintenance when oral phenytoin administration is not possible
Recommended:	Complete Response

1. Introduction and Regulatory History

This is a Class 2 resubmission following a Complete Response on March 22, 2019. The initial NDA submission received a Complete Response because of product quality issues and insufficient support for the clinical safety of the (b) (4) excipient Captisol at the required delivery rate and total dose for the proposed indications.

In this 505(b)(2) submission for Sesquient (Captisol®-Enabled Fosphenytoin Sodium Injection), the applicant again relies on the Agency's prior finding of safety and effectiveness for Cerebyx (the listed drug) and seeks the same indications approved for Cerebyx: treatment of generalized tonic-clonic status epilepticus, prevention and treatment of seizures occurring during neurosurgery, and short-term substitution for oral phenytoin maintenance when oral phenytoin administration is not possible.

In the first submission of this NDA on May 22, 2018. the applicant submitted Chemistry, Manufacturing, and Control (CMC) information, two pivotal bioequivalence (BE) studies which compared Sesquient to Cerebyx (Study 20-A98-AU after IV administration and Study 20-247-SA after IM administration) as well as some nonclinical and clinical safety information for the primary excipient Captisol (sulfobutyl ether betacyclodextrin) to support approval.

The Office of Clinical Pharmacology (OCP) reviewers found the data from the two pivotal BE studies to be adequate to support approval. These two BE studies compared Sesquient to Cerebyx: Study 20-A98-AU (after IV administration) and Study 20-247-SA (after IM

Reference ID: 4537971

administration). Bioequivalence (in terms of plasma phenytoin levels) was demonstrated in both studies, establishing a clinical bridge for Sesquient versus Cerebyx.

The Office of Product Quality (OPQ) review team recommended that the Agency issue a Complete Response Letter to the first submission because it did not include adequate information to ensure that the applicant could consistently manufacture a product that is suitable for the proposed clinical indications.

A number of CMC deficiencies were conveyed to the applicant in a February 26, 2019, CMC Discipline Review (DR) letter regarding the validation of the assessment methods for impurities, product quality information regarding proposed dilution recommendations in labeling, necessary revisions to the USP monograph for fosphenytoin sodium, in-process control testing results for all manufacturing stages of registration batches, and the approach to control for the manufacturing process for the presence of (b) (4) particles. The applicant incompletely responded on February 26, 2019, to the CMC DR Letter. The CMC review team determined that the inability of the applicant to adequately respond to the deficiencies outlined in the DR Letter did not permit for a review during the first review cycle.

The nonclinical reviewers concluded that the nonclinical data in the first NDA submission and available in the Captisol Drug Master File (DMF (# 14364) (for which a letter of authorization was submitted), although having been found to be adequate to support the initiation of adult clinical studies of CE-fosphenytoin, could not support approval without adequate clinical safety data.

The clinical review team concluded that there was a lack of adequate clinical safety data in the first submission to support the safety of the excipient (b) (4) Captisol in the Sesquient formulation. The applicant relied only on the clinical safety data from the BE studies (A98 and 247) provided in the application, the published literature provided in the application, and the Captisol DMF (# 14364) to support the clinical safety of the excipient Captisol. These data either did not contain sufficiently detailed safety data or did not adequately address the dosing frequency, total exposure, and/or a maximum rate of exposure to support the safety of Sesquient for the proposed indication of status epilepticus in any age group. The clinical review team therefore also recommended that a Complete Response action be taken on the first NDA submission.

Given the CMC deficiencies identified and the inadequate clinical safety data with respect to Captisol, a Complete Response letter for the first NDA submission was issued on March 22, 2019.

The current submission is the applicant's Class 2 NDA Resubmission.

2. Review of Class 2 NDA Resubmission

Product Quality Issue:

In its review of the NDA resubmission, the CMC review team continues to conclude that the (b) (4) particulate material identified in Sesquient is a safety hazard.

A teleconference was held with the applicant on November 7, 2019, during which it was determined that the source of the particulates remained unidentified and that a solution to eliminating this impurity was not yet available. A (b) (4) was suggested by the applicant during the teleconference but was deemed by the clinical review team to be impractical for first-responder ambulance and emergency room use in the treatemnt of status epilepticus.

The applicant submitted a quality information amendment on December 6, 2019, which provided additional study results from (b) (4) regarding particles in the drug product. In this amendment, the applicant concluded that the initial particulate information, obtained in association with the (b) (4) testing, was erroneous and not representative of the drug product due to the testing environment conditions. However, the CMC reviewers determined that there is not sufficient information (e.g., documentation of environmental conditions when the (b) (4) testing was performed) to confirm that the initial results from the (b) (4) study are erroneous. Thus, the CMC reviewers concluded that the (b) (4) study report does not conclusively support the applicant's contention that the root cause for the particulates observed and characterized by (b) (4) in Sesquient is laboratory error, and that the (b) (4) results could not be disregarded.

The OPQ team therefore again recommends issuance of a Complete Response Letter. The letter will include a request to the applicant to characterize the particles observed in the drug product and identify the root cause of their presence (e.g., container closure system, testing method/conditions, manufacturing equipment), to provide a Risk Mitigation & Control Plan to mitigate the presence of particulates in Sesquient, and to provide data demonstrating that the actions taken will prevent reoccurrence of particles in Sesquient.

Clinical Safety Issues

During the first review cycle, the applicant was not able to support the clinical safety of the Captisol component of Sesquient for status epilepticus in any age-group. During that cycle, the applicant had proposed reliance on the safety data from the BE studies, Vfend labeling (an off-patent, Captisol-containing antifungal agent approved for patients 12 years of age and older), the published literature, and the Captisol DMF to support its safety.

In his review of the NDA resubmission, the clinical reviewer, Dr. Steven Dinsmore, now finds that the applicant has provided additional support during this review cycle for the use of Captisol at the rapid rate of infusion and the total dose required for the Sesquient indication of status epilepticus for adults but not for children.

Specifically, the applicant now attempts to support the safety of the total dose and rate of administration of Captisol associated with Sesquient during the treatment of status epilepticus in adults by reliance on a paragraph 4[1] patent certification to Carnexiv (a Captisol-containing intravenous formulation of carbamazepine approved for adults), in addition to the Captisol DMF. However, regarding safety of the Captisol infusion in the pediatric population, the applicant's current reliance on a paragraph 2[2] certification for Vfend, the peer-reviewed published literature, and a new report on pediatric use included in the Captisol DMF (#14364) are not adequate to support the rapid rate of infusion required for the treatment of pediatric status epilepticus. The applicant also provided patent certifications for two other approved Captisol-containing products, Baxdela and Zulresso, but these products did not provide any additional support for the use of Sesquient in the pediatric population.

The clinical reviewer therefore indicates that the available safety information supports an approval of Sesquient for adult patients only.

3. Labeling

There were no labeling negotiations during this review cycle.

4. Recommended Regulatory Action

Considering the insufficient response to the product quality previously identified, issuance of a Complete Response letter is again recommended.

[1] patent invalid, unenforceable, or will not be infringed upon
[2] Patent has expired

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/s/

PHILIP H SHERIDAN
12/20/2019 02:25:08 PM

NICHOLAS A KOZAUER
12/20/2019 02:27:58 PM

Summary Memorandum

Date	March 19, 2019
From	Philip H. Sheridan, MD Nick Kozauer, MD Eric Bastings, MD
Subject	Summary Memorandum
NDA#	NDA 210864
Applicant	Sedor Pharmaceuticals, LLC
Date of Submission	May 22, 2018
PDUFA Goal Date	March 22, 2019
Proprietary/ Established (USAN) Name	SESQUIENT (Captisol-enabled fosphenytoin sodium Injection)
Dosage forms / Strength	Solution for intravenous (IV) or intramuscular (IM); (b) (4) and 10ml vial and both at a concentration of 50 mg phenytoin equivalents (PE)/mL
Proposed Indication(s)	Treatment of generalized tonic-clonic status epilepticus, prevention and treatment of seizures occurring during neurosurgery, short-term substitution for oral phenytoin maintenance when oral phenytoin administration is not possible
Recommended:	Complete Response

1. Introduction

In this 505(b)(2) submission for SESQUIENT (Captisol®-Enabled Fosphenytoin Sodium Injection), the applicant (Sedor Pharmaceuticals) relies on the Agency's prior finding of safety and effectiveness for Cerebyx (the listed drug) and is seeking the same indications approved for Cerebyx: treatment of generalized tonic-clonic status epilepticus, prevention and treatment of seizures occurring during neurosurgery, and short-term substitution for oral phenytoin maintenance when oral phenytoin administration is not possible.

The listed drug Cerebyx requires refrigeration for storage. The main potential advantage for SESQUIENT over the listed drug is that room-temperature storage is possible, making it more available for immediate emergency use in the treatment of status epilepticus by first responders in an ambulance or emergency room. This would be clinically significant since the earliest possible initiation of therapy for status epilepticus offers the best chance for a successful therapeutic outcome.

The applicant submitted Chemistry, Manufacturing, and Control (CMC) information, two pivotal bioequivalence (BE) studies which compared SESQUIENT to Cerebyx (Study 20-A98-AU after IV administration and Study 20-247-SA after IM administration) as well as some nonclinical and clinical safety information for the primary excipient Captisol (sulfobutyl ether betacyclodextrin) to support approval.

The following are the key primary reviewers for the SESQUIENT NDA:

CDTL: Angela Men		
RPM: Heather Bullock	**CPMS**: Jackie Ware	
ADRA: Colleen Locicero		
Discipline	**Reviewer**	**TL**
Clinical	Steven Dinsmore	Philip Sheridan
Pharm/Tox	Ed Fisher	Lois Freed
Product Quality (OPQ CMC)	DS: Mouli (Sithamalli Chandramouli) DP: Andrei Ponta EA: Andrei Ponta	ATL: Martha Heimann
	Process: Peter Krommenhoek Facility: Peter Krommenhoek	
	RBPM: Dahlia Walters	
Clinical Pharm	Hristina Dimova	Angela Men
OSIS BEQ	Consult submitted	Shila Nkah (RPM)
OSE	PM: Monique Killen	
OSE/DMEPA	Chad Morris	Lolita White
OSE/DRISK	N/A	N/A
OSE/DEPI	Elisa Braver	Kira Leishear White
OSE/DPV	Karen Long	Allen Brinker
CSS	TBD: Martin Rusinowitz	
	PM: Sandy Saltz	
Labeling	ADL: Tracy Peters	
OPDP	Dhara Shah	Aline Moukhtara

2. CMC

The Office of Product Quality (OPQ) review team recommended that the Agency issue a Complete Response Letter because the application does not include adequate information to ensure that the applicant can consistently manufacture a product that is suitable for the proposed clinical indications.

A number of CMC deficiencies were conveyed to the sponsor in a February 26, 2019, CMC Discipline Review (DR) letter regarding the validation of the assessment methods for impurities, product quality information regarding proposed dilution recommendations in labeling, necessary revisions to the USP monograph for fosphenytoin sodium, in-process control testing results for all manufacturing stages of registration batches, and the approach to control for the manufacturing process for the presence of (b) (4) particles.

Reference ID: 4406198

The applicant incompletely responded on February 26, 2019, to the CMC DR Letter. The CMC review team has determined that the inability of the applicant to adequately respond to the deficiencies outlined in the DR Letter does not permit for a review during the current cycle.

3. Nonclinical Pharmacology/Toxicology

The nonclinical reviewers concluded that the nonclinical data in the current application and available in the Captisol Drug Master File (DMF) (for which a letter of authorization was submitted) are adequate to support initiation of adult clinical studies of CE-fosphenytoin but cannot support approval without adequate clinical safety data. Additionally, the juvenile animal toxicology study of Captisol in the DMF is inadequate by design to support initiation of clinical studies for pediatric patients less than 12 years of age.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) reviewers found the data from the two pivotal BE studies to be adequate to support approval. These two BE studies compared SEQUIENT to Cerebyx: Study 20-A98-AU (after IV administration) and Study 20-247-SA (after IM administration). Bioequivalence (in terms of plasma phenytoin levels) was demonstrated in both studies, establishing a clinical bridge for SESQUIENT versus Cerebyx.

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection of the BE studies is not warranted at this time for the sites listed since they had already been recently evaluated.

5. Efficacy

There was no new clinical efficacy trial required given the results of the BE studies.

6. Clinical Safety

The clinical review team concluded that there is lack of adequate clinical safety data to support the safety of the excipien (b) (4) Captisol® in the SESQUIENT formulation.

The applicant relied on the clinical safety data from the BE studies (A98 and 247) provided in the application, the published literature provided in the application, and the Captisol DMF (# 14364) to support the clinical safety of the excipient Captisol. These data either do not contain sufficiently detailed safety data or do not adequately address the dosing frequency, total exposure, and/or a maximum rate of exposure to support the safety of SESQUIENT for the

proposed indications in any age group. The clinical review team therefore recommends that a Complete Response action be taken.

In response to a consultation from the clinical review team, the Division of Pediatrics and Maternal Health reviewers deferred to the Nonclinical, Clinical, and Clinical Pharmacology review teams regarding the adequacy of safety data for approval of the proposed indications for pediatric or adult patients.

7. Controlled Substance Staff

The Controlled Substance Staff reviewers raised no abuse-potential concerns.

8. Labeling

DMEPA found the proprietary name, SESQUIENT, acceptable from both a promotional and safety perspective. Given that the CMC and clinical safety concerns prevent approval, there were no labeling negotiations during this review cycle.

9. Recommended Regulatory Action

In light of the CMC deficiencies identified and the lack of adequate clinical safety data to support any of the proposed clinical indications, issuance of a Complete Response letter is recommended.

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/s/

PHILIP H SHERIDAN
03/19/2019 07:05:22 PM

NICHOLAS A KOZAUER
03/20/2019 09:57:55 AM

ERIC P BASTINGS
03/21/2019 02:58:42 PM
I concur.