CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210864Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 5, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 210864
Product Name and Strength:	Sesquient (fosphenytoin sodium) injection, 100 mg PE[a] per 2 mL (50 mg PE/mL) 500 mg PE per 10 mL (50 mg PE/mL)
Applicant/Sponsor Name:	Sedor Pharmaceuticals, LLC (Sedor)
OSE RCM #:	2020-1040-2
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

Sedor submitted revised container labels and carton labeling received on November 2, 2020 for Sesquient. The Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling for Sesquient (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

Sedor implemented all our previous recommendation, and we have no additional recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] PE = Phenytoin sodium equivalents
[b] Morris, C. Label and Labeling Review for Sesquient (NDA 210864). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 14. RCM No.: 2020-1040-1.

Reference ID: 4697672

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
11/05/2020 10:18:31 AM

BRIANA B RIDER
11/05/2020 04:06:38 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 22, 2020

To: Heather Bullock, Medical Officer
Division of Neurology II (DN II)

Tina Chhabra, Regulatory Project Manager, DN II

Tracy Peters, Associate Director for Labeling, DN II

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for SESQUIENT (fosphenytoin sodium) injection, for intravenous use

NDA: 210864

In response to the DN II consult request dated June 8, 2020, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for SESQUIENT (fosphenytoin sodium) injection, for intravenous use (Sesquient).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN II (Tina Chhabra) on October 13, 2020 and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 2, 2020, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Koung Lee (240) 402-8686 or Koung.lee@fda.hhs.gov.

33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4690380

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KOUNG U LEE
10/22/2020 02:24:08 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 14, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 210864
Product Name and Strength:	Sesquient (fosphenytoin sodium) injection, 100 mg PE[a] per 2 mL (50 mg PE/mL) 500 mg PE per 10 mL (50 mg PE/mL)
Applicant/Sponsor Name:	Sedor Pharmaceuticals, LLC (Sedor)
OSE RCM #:	2020-1040-1
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

Sedor submitted revised container labels and carton labeling received on October 2, 2020 for Sesquient. The Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling for Sesquient (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 ASSESMENT AND RECOMMENDATIONS

Table 1 identifies our medication error concerns with the container labels, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

[a] PE = Phenytoin sodium equivalents
[b] Morris, C. Label and Labeling Review for Sesquient (NDA 210864). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 10. RCM No.: 2020-1040.

Reference ID: 4685412

Table 1. Identified Issues and Recommendations for Sedor Pharmaceuticals, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
			(b) (4)
Container Labels			
			(b) (4)

[c] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

Table 1. Identified Issues and Recommendations for Sedor Pharmaceuticals, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
(b) (4)			

3 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. Above, we have provided recommendations in Table 1 for Sedor. We ask that the Division convey Table 1 in its entirety to Sedor, so the recommendations are implemented prior to approval of this NDA.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
10/14/2020 10:46:00 AM

BRIANA B RIDER
10/14/2020 11:59:05 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 10, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 210864
Product Name and Strength:	Sesquient (fosphenytoin sodium) injection, 100 mg PE[a] per 2 mL (50 mg PE/mL) 500 mg PE per 10 mL (50 mg PE/mL)
Applicant/Sponsor Name:	Sedor Pharmaceuticals, LLC (Sedor)
OSE RCM #:	2020-1040
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

Sedor submitted a Class 2 Resubmission on May 8, 2020 for Sesquient. The Division of Neurology 2 (DN 2) requested that we review the proposed Prescribing Information (PI), container labels and carton labeling for Sesquient (Appendix A) to determine if they are acceptable from a medication error perspective.

2 REGULATORY HISTORY

NDA 210864 is a 505(b)(2) NDA and the listed drug product is Cerebyx, NDA 020450. Sedor submitted the original NDA 210864 on May 22, 2018, and we performed a label and labeling review[b] of the submission during that review cycle. However, the application received a complete response (CR) on March 22, 2019[c]; our recommendations for the labels and labeling were sent to Sedor in the CR Letter.

[a] PE = Phenytoin sodium equivalents
[b] Morris, C. Label and Labeling Review for Sesquient (NDA 210864). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JAN 08. RCM No.: 2018-1316.
[c] March 22, 2018 CR Letter available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804e60e3&_afrRedirect=2710071592313948

Reference ID: 4654187

On June 28, 2019, Sedor submitted a Class 2 Resubmission, and we performed a label and labeling review[d] of the submission during that review cycle. However, the application received a complete response (CR) on December 20, 2019[e]; our recommendations for the labels and labeling were sent to Sedor in the CR Letter.

Therefore, on May 08, 2020, Sedor submitted a Class 2 Resubmission, which is the subject of this review.

3 ASSESSMENT

Tables 1 and 2 identify our medication error concerns with the PI, container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 1. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	We note, throughout the PI, the 100 mg PE/2 mL packaging is described as a (b) (4) single-dose vial (containing 2 mL) in the PI.	To describe the vial size as (b) (4) mL in the labeling may lead to confusion of what actual volume of drug product is contained in the vial and contribute to preparation and dosing errors.	We defer to the Office of Pharmaceutical Quality (OPQ) to review and clarify the description of the package size for the 100 mg PE/2 mL packaging.
2.	Numeric doses are not consistently expressed with a corresponding unit of measure.	We are concerned that this may lead to confusion of dose.	We recommend each numeric dose have a corresponding unit of measure after the numeric value (e.g., revise '10 to 20 mg/kg' to read '10 mg/kg to 20 mg/kg').
3.	The (b) (4) re used to denote the routes of administration.	Can be improved for clarity.	We recommend the (b) (4) be spelled out throughout the dosage and administration section of the highlights of PI and full PI, or at least upon

[d] Morris, C. Label and Labeling Review for Sesquient (NDA 210864). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 24. RCM No.: 2018-1316-1.

[e] December 20, 2019 CR Letter available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80532656&_afrRedirect=2710019914480669

Table 1. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			first use.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The statement "(b) (4) [redacted] in Section 2.2 can be improved.	Readability can be improved.	We recommend the statement "(b) (4) [redacted]" be revised to read "The diluted Sesquient solution is stable for 4 hours at room temperature" or similar.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The dash symbol "-" to designate the temperature range (i.e., 15-30°C) is present.	Clarity can be improved to reduce the risk for misinterpretation and degraded product medication errors.	We recommend the dash symbol "-" be replaced with the word "to".
2.	The temperature unit of measure, °C or °F, is not presented after each numeric digit in the storage statement.	Clarity can be improved to reduce the risk for misinterpretation and degraded product medication errors.	We recommend the temperature unit of measure (°C or °F) be presented after each numeric digit in the storage statement.
3.	The labeler code within the National Drug Code (NDC) is denoted by a placeholder (i.e., XXXX).	Should reflect the actual NDC number.	We recommend the placeholder for the labeler code be revised to reflect the actual number.

Table 2. Identified Issues and Recommendations for Sedor (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
(b) (4) [redacted]			

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Table 2. Identified Issues and Recommendations for Sedor (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			(b) (4)

4 CONCLUSION

Our evaluation of the proposed Sesquient PI, container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 1 for the Division and Table 2 for Sedor. We ask that the Division convey Table 2 in its entirety to Sedor, so the recommendations are implemented prior to approval of this NDA.

APPENDIX A. LABELS AND LABELING

A.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Sesquient labels and labeling submitted by Sedor on May 8, 2020.

- Container labels
- Carton labeling
- Prescribing Information (Image not shown), available at: \\CDSESUB1\evsprod\nda210864\0029\m1\us\114-label\1141-draft-label\proposed.docx

A.2 Label and Labeling Images

Container labels

(b) (4)

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
08/10/2020 02:27:27 PM

BRIANA B RIDER
08/10/2020 10:17:52 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 24, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 210864
Product Name and Strength:	Sesquient (fosphenytoin sodium) injection, 100 mg PE[a] per 2 mL (50 mg PE/mL) 500 mg PE per 10 mL (50 mg PE/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sedor Pharmaceuticals, LLC
FDA Received Date:	June 28, 2019
OSE RCM #:	2018-1316-1
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader (Acting):	Briana Rider, PharmD, CPPS

[a] PE = Phenytoin sodium equivalents

Reference ID: 4496244

1 REASON FOR REVIEW

As part of the review process for Sesquient (fosphenytoin sodium) injection, NDA 210864, the Division of Neurology Products (DNP) requested we review the proposed Sesquient Prescribing Information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

NDA 210864 is a 505(b)(2) NDA and the listed drug product is Cerebyx, NDA 020450. Sedor submitted the original NDA 210864 on May 22, 2018, and we performed a label and labeling review of the submission during that review cycle. However, the application received a complete response (CR) on March 22, 2019; our recommendations for the labels and labeling were sent to Sedor in the CR Letter. Therefore, on June 28, 2019, Sedor submitted a Class 2 Resubmission.

1.2 PRODUCT INFORMATION

The proposed Sesquient (fosphenytoin sodium) product is comprised of fosphenytoin sodium, USP, and a primary excipient sulfobutyl ether beta-cyclodextrin (i.e., Captisol®) (b) (4)

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

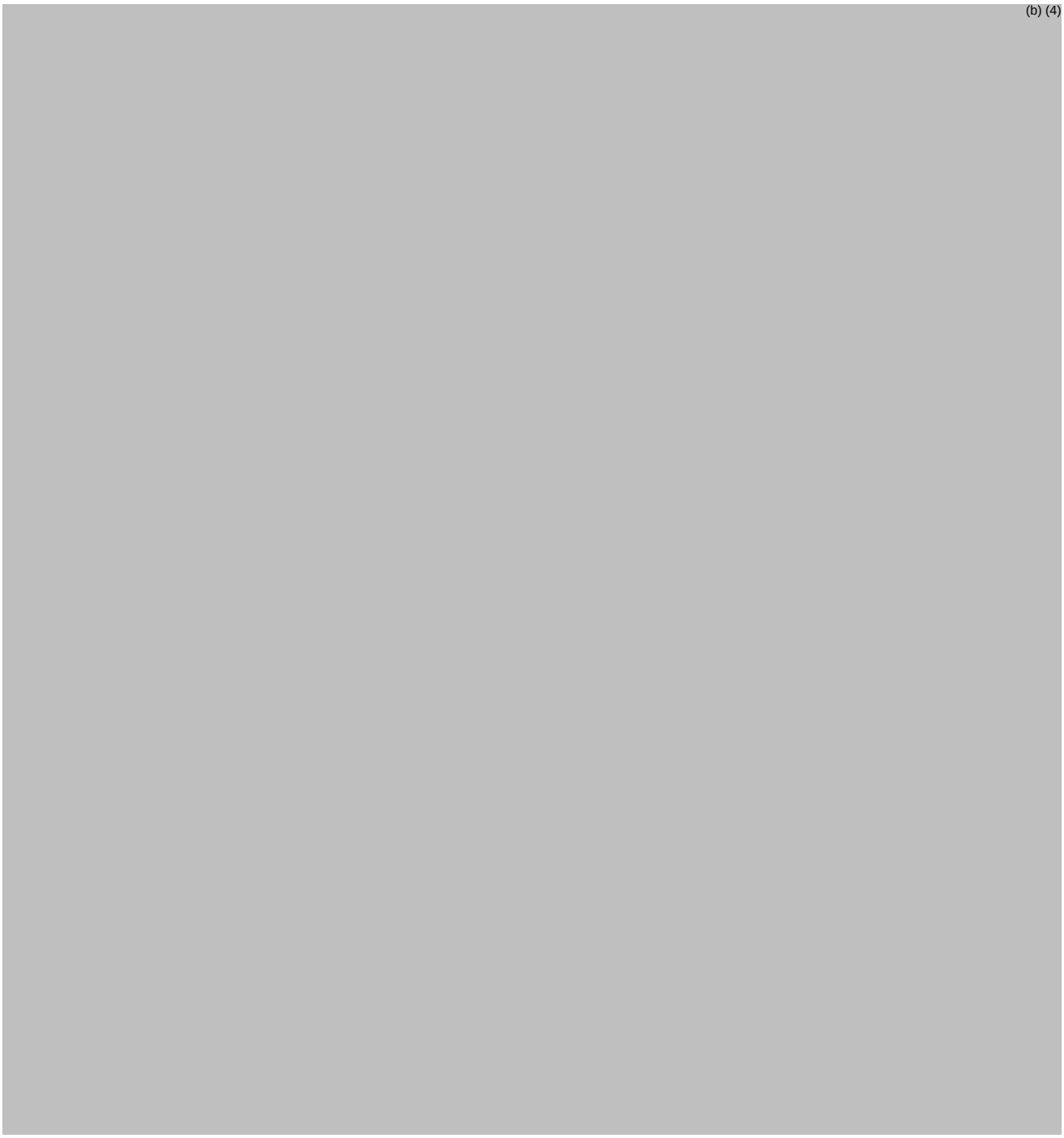
N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below identifies our medication error concerns with the Prescribing Information (PI), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology Products (DNP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	We note, throughout the PI, the 100 mg PE/2 mL packaging is described as a (b) (4) single-dose vial (containing 2 mL) in the PI.	To describe the vial size as (b) (4) mL in the labeling may lead to confusion of what actual volume of drug product is contained in the vial and contribute to preparation and dosing errors.	We defer to the Office of Pharmaceutical Quality (OPQ) to review and clarify the description of the package size for the 100 mg PE/2 mL packaging.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The statement "(b) (4) in Section 2.2 can be improved.	Readability can be improved.	We recommend the statement (b) (4) " be revised to read "The diluted Sesquient solution is stable for 4 hours at room temperature" or similar.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The NDC numbers are not presented.	We cannot assess for risk of product selection medication errors.	We recommend the sponsor define the NDC number per 21 CFR 207.33 and update the PI accordingly.
2.	The dash symbol "-" to designate the temperature range (i.e., 15-30°C) is present.	Clarity can be improved to reduce the risk for misinterpretation and degraded product medication errors.	We recommend the dash symbol "-" be replaced with the word "to".
3.	The temperature unit of measure, °C or °F, is not presented after each numeric digit in the storage statement.	Clarity can be improved to reduce the risk for misinterpretation and degraded product medication errors.	We recommend the temperature unit of measure (°C or °F) be presented after each numeric digit in the storage statement.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



4 CONCLUSION

Our evaluation of the proposed Sesquient Prescribing Information (PI), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Sedor Pharmaceuticals, LLC so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Sesquient that Sedor Pharmaceuticals, LLC submitted on June 28, 2019, and the listed drug (LD), Cerebyx[b].

Table 4. Relevant Product Information for Listed Drug and Sesquient

Product Name	Cerebyx	Sesquient
Initial Approval Date	August 5, 1996 (NDA 020450)	N/A
Active Ingredient	fosphenytoin sodium	fosphenytoin sodium
Indication	Treatment of generalized tonic-clonic status epilepticus. Prevention and treatment of seizures occurring during neurosurgery. As a substitution, short-term use, for oral phenytoin.	Treatment of generalized tonic-clonic status epilepticus. Prevention and treatment of seizures occurring during neurosurgery. As a substitution, short-term use, for oral phenytoin.
Route of Administration	Intravenous infusion, Intramuscular	Intravenous infusion, Intramuscular
Dosage Form	Injection	injection
Strength	50 mg phenytoin sodium equivalents (PE)/mL	50 mg phenytoin sodium equivalents (PE)/mL
Dose and Frequency	Loading Dose <u>Status Epilepticus</u> *Adults* 15 mg PE/kg to 20 mg PE/kg at a rate of 100 mg PE/min to 150 mg PE/min. *Pediatric (<17 years old)* 15 mg PE/kg to 20 mg PE/kg at a rate of 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower). <u>Non-Emergent</u> *Adults* 10 mg PE/kg to 20 mg PE/kg	Loading Dose <u>Status Epilepticus</u> *Adults* 15 mg PE/kg to 20 mg PE/kg at a rate of 100 mg PE/min to 150 mg PE/min. *Pediatric (<17 years old)* 15 mg PE/kg to 20 mg PE/kg at a rate of 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower). <u>Non-Emergent</u> *Adults* 10 mg PE/kg to 20 mg PE/kg

[b] Cerebyx [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 SEP 13. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020450s037s038lbl.pdf

	given IV at a rate no greater than 150 mg PE/min or IM. *Pediatric (<17 years old)* 10 mg PE/kg to 15 mg PE/kg at a rate of 1 mg PE/kg/min to 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower). Maintenance Dose *Adults* 4 mg PE/kg/day to 6 mg PE/kg/day in divided doses at a rate no greater than 150 mg PE/min. *Pediatric (<17 years old)* 2 mg PE/kg to 4 mg PE/kg which should be given 12 hours after the loading dose and then continued every 12 hours (4 mg PE/kg/day to 8 mg PE/kg/day in divided doses) at a rate of 1 mg PE/kg/min to 2 mg PE/kg/min (or 100 mg PE/min, whichever is slower).	given IV at a rate no greater than 150 mg PE/min or IM. *Pediatric (<17 years old)* 10 mg PE/kg to 15 mg PE/kg at a rate of 1 mg PE/kg/min to 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower). Maintenance Dose *Adults* 4 mg PE/kg/day to 6 mg PE/kg/day in divided doses at a rate no greater than 150 mg PE/min. *Pediatric (<17 years old)* 2 mg PE/kg to 4 mg PE/kg which should be given 12 hours after the loading dose and then continued every 12 hours (4 mg PE/kg/day to 8 mg PE/kg/day in divided doses) at a rate of 1 mg PE/kg/min to 2 mg PE/kg/min (or 100 mg PE/min, whichever is slower).
How Supplied	100 mg PE/2 mL single-dose vial Carton containing 1 or 25 vials 500 mg PE/10 mL single-dose vials Carton containing 1 or 10 vials	100 mg PE/2 mL single-dose vial Carton containing 25 vials 500 mg PE/10 mL single-dose vials Carton containing 10 vials
Storage	Store under refrigeration at 2°C to 8°C (36°F to 46°F). The product should not be stored at room temperature for more than 48 hours.	Store at room temperature. Temperature excursions are permitted between 15-30°C (59-86°F). [see USP Controlled Room Temperature].
Container Closure	Glass vial	Glass vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 13, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Sesquient, NDA 210864, Captisol, and fosphenytoin. Our search identified our review[c] of labels and labeling from the original submission. As noted above, the recommendations contained within that review were communicated to Sedor in the CRL. We confirmed our recommendations were considered or implemented.

[c] Morris, C. Label and Labeling Review for Sesquient (Captisol-enabled fosphenytoin sodium) (NDA 210864). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JAN 08. RCM No.: 2018-1316.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Sesquient labels and labeling submitted by Sedor Pharmaceuticals, LLC on June 28, 2019.

- Container labels
- Carton labeling
- Prescribing Information (Image not shown)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
09/24/2019 10:33:18 AM

BRIANA B RIDER
09/25/2019 09:26:52 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

From:	Ethan D. Hausman, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Hari Cheryl Sachs, MD, Medical Team Leader
NDA Number:	210,864
Sponsor:	Sedor Pharmaceuticals, LLC
Drug:	Sesquient (captisol-enabled fosphenytoin) injection
Indication:	Generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery; can also be substituted, as short-term use, for oral phenytoin; should be used only when oral phenytoin administration is not possible
Dosage Form and Route of Administration:	Solution for injection
Pediatric Dosing:	Refer to labeling for reference drug Cerebyx (fosphenytoin sodium, NDA 20,450); also see below.
Division Consult Request:	The Division of Neurology Products (DNP) requests DPMH assistance in reviewing the safety of the captisol component of the candidate drug. [The candidate drug application is received as a 505(b)(2) application; the reference drug is Cerebyx (fosphenytoin sodium, NDA 20,450)].

Background

This memo is in response to a consult from the Division of Neurology Products (DNP) to request the Division of Pediatric and Maternal Health's (DPMH's) assistance for premarket review of NDA (b) (4) (proposed name Sesquient), a fosphenytoin product containing captisol. The application has been submitted aa a 505(b)(2) application and the reference drug is Cerebyx (fosphenytoin sodium; NDA 20,450).

The consult requests that DPMH "help determine if currently available nonclinical and clinical pediatric safety data and published clinical pediatric experience with captisol-containing products will allow approval of Sesquient a captisol-enabled fosphenytoin sodium for injection) for pediatric patients below age 12 years. If so, what is the appropriate lower age limit?" The sponsor proposes "a pediatric indication down to age 2 years (the same as the Cerebyx indication). The issue is whether there are sufficient pediatric safety data (nonclinical and clinical) for pediatric subjects less than 12 years of age."

Per the consult request, DPMH input is requested regarding the safety of the captisol component only, rather than the fosphenytoin component. The consult request specifies DPMH pay attention specifically to the following proposed labeling:

(b) (4)

DPMH Comments

Captisol is a specific type of a family of molecules referred to as cyclodextrins.

DPMH identified five drugs approved (b) (4) which contain cyclodextrins. On review of available labeling and pre-clinical reviews for these products [including any available clinical pharmacology (Clin Pharm) and pharmacotoxicology (Pharm-tox) reviews], DPMH identified one potentially common safety issue, renal toxicity, which may be enhanced in patients younger than 2 years due to physiologic immaturity.

1. Bridion (sugammadex, **NDA 22,225**). This is a neuromuscular blockade reversal agent which contains a "modified gamma-cyclodextrin" per the clinical pharmacology review. Current labeling and the Pharm-tox review both include juvenile toxicity information. (b) (4)
2. Dyloject (diclofenac, **NDA 22,396**). This drug is approved for adults only for treatment of mild to moderate pain, and in adults only for treatment of severe pain combination with and opioid. DPMH identified no discussion in NDA labeling about dextrins, cyclodextrins, or captisol; however, the premarket review for

Reference ID: 4376477

NDA 22,396 contains a description of juvenile toxicity and states that additional juvenile-toxicology data are needed (b) (4) for patients 1 year to less than 2 years. That same review does not mention if any additional toxicology studies were needed (b) (4) in patients 2 years to less than 17 years.

3. Vibativ (telavancin hydrochloride, **NDA 22,110**). This antibiotic approved in adults only. Labeling states that "cyclodextrin is excreted in urine and may accumulate in patients with renal impairment. Serum creatinine should be closely monitored and, if renal toxicity is suspected, an alternative agent should be considered." A PMHS (now DPMH) review noted that preclinical toxicity program showed limb malformation in offspring of dams which was likely drug related (drug vs cyclodextrin). (b) (4) The agency requested studies in patients 0 to 17 years with protocol(s) to be submitted in 2014; however, studies in patients younger than 17 years have been deferred.

4. Baxdela (Delafloxacin, **NDAs 208,610 and 208,611**). This fluoroquinolone antibiotic is approved in adults only and contains sulfobutylether-B-cyclodextrin. The Pharm-tox review discusses juvenile toxicity studies in beagles (11 weeks old) which showed quinolone associated arthropathy/chondropathy. Pediatric studies were waived for known quinolone issues in pediatric patients.

5. Noxafil (posaconazole, multiple **NDAs 22,003, 22,027, 205,503, and 205,596**). DPMH is aware that captisol/cyclodextrin (b) (4) however current labeling does not address captisol or cyclodextrins. DPMH is unable to locate relevant Pharm-tox reviews. Note: NDA 22,003, has deferred pediatric studies for patients 0 to 12 years, NDA 22,027 has deferred pediatrics studies for patients 0 to 16 years, and NDAs 205,503 and 205,596 have deferred studies in patients 2 to <18 years (waived in 0 to <2 years). If DNP has additional questions related to the toxicology program for this drug, DPMH recommends DNP direct further questions to the Pharm-tox review for the NDAs and their corresponding INDs.

DPMH additionally identified a single review article summarizing the safety of cyclodextrins including captisol [De Schaepdrijver L, Marien D, Rhimi C, et al. Juvenile animal testing of hydroxypropyl-B-cyclodextrin in support of pediatric drug development. Reproductive Toxicology. 2015. 56: 87-96.]. (Note: The several individual studies that were identified are all included in De Schaepdrijver et al and are not individually addressed in this memo). De Schaepdrijver et al conclude that there is a paucity of both juvenile toxicology data relevant to humans under approximately 5 years of age, and a paucity of safety data in humans younger than approximately 5 years. Nevertheless, DPMH notes the rat study discussed in the publication identified an 'osmotic nephrosis' and loose stools related to water retention in the large intestine but that no "unexpected" toxicology findings were noted.

Conclusions and Recommendations

1) Because captisol may adversely renal function in juvenile animal models, and possibly in young patients as well, DNP, Pharm-tox, Clinical Pharmacology

Reference ID: 4376477

should establish if labeling changes for children with impaired renal function may be justified.

2) Review of the description and adequacy juvenile rat study described in the consult is deferred to the Pharm-tox team.

3) Further review and comment on the appropriateness of the safety of the dosing rationale is deferred to Pharm-tox and Clin Pharm.

4) DNP should re-consult DPMH if additional pediatric-related issues arise.

Reference ID: 4376477

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ETHAN D HAUSMAN
01/16/2019 08:23:09 AM

HARI C SACHS
01/16/2019 11:02:16 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 8, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 210864
Product Name and Strength:	Sesquient (Captisol®-Enabled Fosphenytoin Sodium) injection, 50 mg phenytoin sodium equivalents (PE)/mL, (500 mg PE/10 mL, 100 mg PE/2 mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sedor Pharmaceuticals, LLC (Sedor)
FDA Received Date:	May 22, 2018
OSE RCM #:	2018-1316
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

Reference ID: 4372813

1 REASON FOR REVIEW

The Division of Neurology Products (DNP) requested we review the proposed Prescribing Information (PI), container labels, and carton labeling for NDA 210864 Sesquient (Captisol®-Enabled Fosphenytoin Sodium) for areas of vulnerability that may increase the risk for medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed Prescribing Information (PI), container labels, and carton labeling identified the following areas that can be improved.

Prescribing Information (PI)

Section 16 How Supplied/Storage and Handling

- The NDC numbers are not presented for Agency review and may contribute to product selection medication errors.
- The symbol "-" to designate the temperature range is present, which may be misinterpreted and lead to degraded product medication error.
- The temperature unit of measure, °C or °F, is not presented after each digit in the storage statement which may lead to confusion and lead to degraded drug product medication error

Carton labeling and container label

Reference ID: 4372813

We provide recommendations regarding these areas below in Section 4.1 and Section 4.2 in order to help minimize the potential for medication errors to occur with the use of the product.

During our review of the labeling for NDA 210864, we note within the PI labeling the 100 mg PE/2 mL packaging is described as a (b) (4) single-dose vial (containing 2 mL). To describe the vial size as (b) (4) in the labeling may lead to confusion of what actual volume of drug product is contained in the vial and contribute to dispensing and dosing errors. Specifically, we note this description throughout the PI labeling (e.g. HPI Dosage Forms and Strengths, Section 2.1 Important Administration Instructions to Avoid Dosing Errors, Section 3 Dosage Forms and Strengths, Section 5.1 Dosing Errors, Section 11 Description, and Section 16.1 How Supplied). We defer to the Office of Pharmaceutical Quality (OPQ) to review and clarify the description of the package size for the 100 mg PE/2 mL packaging.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the proposed labels and labeling where information can be improved or added to help ensure the safe and effective use of this product We provide recommendations below in section 4.1 for the division and in section 4.2 for the Sponsor to address our concerns. We advise these recommendations are implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

- How Supplied/Storage and Handling Section

Reference ID: 4372813

- The NDC numbers are not presented for Agency review and are denoted as placeholders on the carton labeling and container label. We recommend the sponsor define the NDC number per 21 CFR 207.33 and update the PI accordingly.
- The symbol "-" to designate the temperature range is present, which may be misinterpreted and lead to degraded drug product medication error. We recommend the sponsor replace the symbol "-" with the word "to"
- The temperature unit of measure, °C or °F, is not presented after each digit, which may lead to confusion and lead to degraded drug product medication error. We recommend the sponsor assure the temperature unit of measure is presented after each digit.

4.2 RECOMMENDATIONS FOR SEDOR PHARMACEUTICALS, LLC

We recommend the following be implemented prior to approval of this NDA:

Carton labeling and container label

Container labels

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Sesquient received on May 22, 2018 from Sedor Pharmaceuticals, LLC, and the listed drug (LD).

Table 2. Relevant Product Information for Sesquient and the Listed Drug		
Product Name	Sesquient	Cerebyx[a]
Initial Approval Date	N/A	August 5, 1996 (NDA 020450)
Active Ingredient	Captisol®-Enabled Fosphenytoin Sodium	fosphenytoin sodium
Indication	Treatment of generalized tonic-clonic status epilepticus. Prevention and treatment of seizures occurring during neurosurgery. As a substitution, short-term use, for oral phenytoin.	Treatment of generalized tonic-clonic status epilepticus. Prevention and treatment of seizures occurring during neurosurgery. As a substitution, short-term use, for oral phenytoin.
Route of Administration	Intravenous infusion, Intramuscular	Intravenous infusion
Dosage Form	injection	Injection
Strength	50 mg phenytoin sodium equivalents (PE)/mL	50 mg phenytoin sodium equivalents (PE)/mL
Dose and Frequency	Loading Dose Status Epilepticus *Adults* 15 mg PE/kg to 20 mg PE/kg at a rate of 100 mg PE/min to 150 mg PE/min. *Pediatric (<17 years old)* 15 mg PE/kg to 20 mg PE/kg at a rate of 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower). Non-Emergent *Adults* 10 mg PE/kg to 20 mg PE/kg	Loading Dose Status Epilepticus *Adults* 15 mg PE/kg to 20 mg PE/kg at a rate of 100 mg PE/min to 150 mg PE/min. *Pediatric (<17 years old)* 15 mg PE/kg to 20 mg PE/kg at a rate of 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower). Non-Emergent *Adults* 10 mg PE/kg to 20 mg PE/kg

[a] Cerebyx [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2017 DEC 31. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020450s037s038lbl.pdf

	given IV at a rate no greater than 150 mg PE/min or IM. *Pediatric (<17 years old)* 10 mg PE/kg to 15 mg PE/kg at a rate of 1 mg PE/kg/min to 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower). Maintenance Dose *Adults* 4 mg PE/kg/day to 6 mg PE/kg/day in divided doses at a rate no greater than 150 mg PE/min. *Pediatric (<17 years old)* 2 mg PE/kg to 4 mg PE/kg which should be given 12 hours after the loading dose and then continued every 12 hours (4 mg PE/kg/day to 8 mg PE/kg/day in divided doses) at a rate of 1 mg PE/kg/min to 2 mg PE/kg/min (or 100 mg PE/min, whichever is slower).	given IV at a rate no greater than 150 mg PE/min or IM. *Pediatric (<17 years old)* 10 mg PE/kg to 15 mg PE/kg at a rate of 1 mg PE/kg/min to 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower). Maintenance Dose *Adults* 4 mg PE/kg/day to 6 mg PE/kg/day in divided doses at a rate no greater than 150 mg PE/min. *Pediatric (<17 years old)* 2 mg PE/kg to 4 mg PE/kg which should be given 12 hours after the loading dose and then continued every 12 hours (4 mg PE/kg/day to 8 mg PE/kg/day in divided doses) at a rate of 1 mg PE/kg/min to 2 mg PE/kg/min (or 100 mg PE/min, whichever is slower).
How Supplied	100 mg PE/2 mL single-dose vial Carton containing 1 or 25 vials 500 mg PE/10 mL single-dose vials Carton containing 1 or 10 vials	100 mg PE/2 mL single-dose vial Carton containing 1 or 25 vials 500 mg PE/10 mL single-dose vials Carton containing 1 or 10 vials
Storage	Store at room temperature. Temperature excursions are permitted between 15-30°C (59-86°F). [see USP Controlled Room Temperature].	Store under refrigeration at 2°C to 8°C (36°F to 46°F). The product should not be stored at room temperature for more than 48 hours.
Container Closure	Glass vial	Glass vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 10, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, Sesquient, NDA 210864, Captisol, and fosphenytoin. Our search did not identify any previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Sesquient labels and labeling submitted by Sedor Pharmaceuticals, LLC on May 22, 2018.

- Container label
- Carton labeling
- Prescribing Information (Image not shown)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
01/08/2019 09:54:44 AM

LOLITA G WHITE
01/08/2019 10:20:36 AM

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date:	December 12, 2018
To:	Billy Dunn, M.D., Director Division of Neurology Products
Through:	Dominic Chiapperino, Ph.D., Director Controlled Substance Staff
From:	Martin Rusinowitz, M.D., Senior Medical Officer Controlled Substance Staff
Subject:	**Name:** Captisol-enabled fosphenytoin sodium injection **NDA:** 210864 **Indication:** Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery **Dosages:** **Adult loading dose:** 15 to 20 mg PE/kg at a rate of 100 to 150 mg PE/min **Pediatric loading dose:** 15 to 20 mg PE/kg at a rate of 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower) **Sponsor:** Sedor Pharmaceuticals, LLC
Materials Reviewed:	Sponsor's Introduction: Module 2.2 Sponsor's Clinical Overview: Module 2.5 Sponsor's Clinical Summary: Module 2.7 NDA 20450, Cerebyx

Background

This memorandum is to document the advice the Controlled Substance Staff (CSS) provided to the Division of Neurology Products (DNP) in preparation for the NDA 210864 filing date of

Reference ID: 4362498

7/21/2018, after a Pre-NDA meeting with Sedor Pharmaceuticals, under IND 74871, held on 7/6/2017. CyDex Pharmaceuticals originally filed IND 74871 on 9/24/2007. Ligand Pharmaceuticals acquired CyDex on 1/26/2011. Subsequently, Sedor acquired the rights to license Captisol-enabled fosphenytoin on 12/7/2015.

The IND development program is for Captisol-enabled fosphenytoin (CE-Fosphenytoin), a drug product comprised of fosphenytoin sodium and a primary excipient sulfobutyl ether beta-cyclodextrin (Captisol) (b) (4) room-temperature storage of the drug product at a more physiologic pH of 7(b) (4)–8.2.

NDA 210864 is for CE-Fosphenytoin Injection via the 505(b)(2) regulatory pathway. The Sponsor is relying on the Agency's findings of safety and efficacy for the fosphenytoin sodium injection Reference Listed Drug (RLD) Cerebyx (NDA 020450) to support the safety and efficacy of CE-Fosphenytoin. The proposed indication is for the 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. It should be used only when oral phenytoin administration is not possible. CE-Fosphenytoin is expected to be used as second-phase therapy upon arrival at the hospital emergency room or in the intensive care unit. It is intended for intravenous (IV) and intramuscular (IM) injection.

Fosphenytoin, the active ingredient in CE-Fosphenytoin, is a prodrug that is rapidly converted to the active metabolite phenytoin by phosphatases found in a number of tissues. Consequently, the anticonvulsant activity of CE-Fosphenytoin is ultimately based on the activity of 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.

Conclusions

Fosphenytoin Sodium Injection, Cerebyx, was approved as a parenteral anti-epileptic drug (AED) on 12/26/1996. Diphenylhydantoin, Dilantin, was made in 1908 and was subsequently found to be an effective AED in 1938. It was approved as an anticonvulsant by the FDA in 1953. Although most of the numerous clinical trials involving Cerebyx and Dilantin don't meet today's rigorous study designs used for abuse potential investigations, there has never been an issue with abuse-related adverse events (AEs) such as euphoria, feeling drunk, or elevated mood. A review of the published medical literature, with particular attention to neuropsychiatric AEs, has failed to uncover any signal to suggest abuse potential of diphenylhydantoin or fosphenytoin.

Recommendations to the Division

Based on our review of Cerebyx's and Dilantin's original NDAs, along with the published medical literature for more than the last 65 years, CE-Fosphenytoin does not have any abuse-

Reference ID: 4362498

related concerns. CSS requests the Division to consult us if the DNP review team identifies any such concerns associated with the drug through the course of their review.

Reference ID: 4362498

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTIN S RUSINOWITZ
12/12/2018

DOMINIC CHIAPPERINO
12/12/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11/19/2018

TO: Division of Neurology Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 210864

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The concerns outlined in the consult submitted to OSIS on June 25, 2018 can be directly addressed by contacting the applicant to obtain copies of the original clinical study reports to evaluate the formatting updates and determine whether reissuance of the study reports impacts the integrity of the data.

The CEDRA San Antonio, TX and Austin, TX sites are no longer in operation.

The Office of Regulatory Affairs (ORA) inspected the sites in October 2007 and August 2008. The inspections were conducted under the following submissions: NDAs (b) (4).

The final classification for the inspections conducted in October 2007 and August 2008 was Voluntary Action Indicated (VAI); however, the Division of Scientific Investigations (now known as OSIS) determined that the inspectional findings were not likely to impact the audited studies.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	CEDRA Clinical Research, LLC.	2455 NE Loop 410, Suite 150, San Antonio, TX
Clinical	CEDRA Clinical Research, LLC.	8501 N. Mopac Expressway, Suite 200, Austin, TX

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANGEL S JOHNSON
11/21/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 8/1/2018

TO: Division of Neurology Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to Insepect Memo**

RE: NDA 210864

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) declines to conduct the inspection of the sites below. The rationale for this decision is noted below:

1. Specific details regarding the discrepancies identified with both bioequivalence studies, 20-247-SA and 20-A98-AU were not provided in the consult.
2. The CEDRA Austin and CEDRA San Antonio sites are no longer in operation.
3. The availability of the original CEDRA clinical and analytical study reports is uncertain.

We recommend that you contact the applicant to obtain copies of the original clinical and analytical study reports to evaluate the formatting updates and determine whether reissuance of the study reports impacts the integrity of the data.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	CEDRA Clinical Research, LLC.	2455 NE Loop 410, Suite 150, San Antonio, TX
Clinical	CEDRA Clinical Research, LLC.	8501 N. Mopac Expressway, Suite 200, Austin, TX

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHILA S NKAH
08/02/2018