

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210864Orig1s000

OTHER ACTION LETTERS



NDA 210864

COMPLETE RESPONSE

Sedor Pharmaceuticals, LLC
Attention: Rick Lampe
Director of Regulatory Affairs & Quality Assurance
1800 East Lancaster Avenue, Suite N
Paoli, PA 19301

Dear Mr. Lampe:

Please refer to your new drug application (NDA) dated and received May 22, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sesquient (fosphenytoin sodium) injection, 100 mg and 500 mg phenytoin sodium equivalents/ml.

We acknowledge receipt of your amendment dated June 28, 2019, which constituted a complete response to our March 22, 2019, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Product Quality

It is crucial from a safety perspective that the drug product does not contain foreign particles. Information provided to date has not adequately addressed this drug product quality issue.

In a quality information amendment submitted on December 6, 2019, you provided additional study results from (b) (4) regarding particles in the drug product. You concluded that the initial particulate information, obtained in association with the (b) (4) testing at (b) (4), was erroneous and not representative of the drug product due to testing environment conditions. However, there is not sufficient information (e.g., documentation of environmental conditions at (b) (4) when the (b) (4) testing was performed) to confirm that the initial results from the (b) (4) study are erroneous. Thus, the (b) (4) study report does not conclusively support your contention that the root cause for the particulates observed and characterized by (b) (4) in your drug product is laboratory error, and we are unable to disregard the (b) (4) results.

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), and provide a Risk Mitigation & Control Plan to mitigate the presence of particulates in your drug product. Provide data demonstrating that the actions taken will prevent reoccurrence of particles in the drug product.

Regulatory

Your original application submitted May 22, 2018, relied on, in part, FDA's finding of safety and effectiveness for Parke Davis's NDA 020450 for Cerebyx (fosphenytoin sodium) injection. Our March 22, 2019, complete response (CR) letter included, among other deficiencies, the clinical deficiency "Lack of Adequate Information to Support the Safety of Captisol". To address this deficiency, the cover letter for your June 28, 2019, resubmission (RS) to our CR letter stated "For additional Captisol safety data, Sedor is also relying on the Agency's previous findings of safety for the following RLDs: Baxdela™ (NDA 208611), Carnexiv™ (NDA 206030), Vfend® (NDA 021267), and Zulresso™ (NDA 211371)". Additionally, Field 20 of your June 28, 2019, FDA form 356h identified these NDAs, in addition to Cerebyx NDA 020450, as the basis for your 505(b)(2) (re)submission.

1. Based on our review of your application and your June 28, 2019 RS, we have determined that reliance on Lundbeck Pharmaceuticals' NDA 206030 for Carnexiv (carbamazepine) solution is needed to justify the safety of the Captisol excipient. We also note that you have a letter of authorization for DMF 14364. Please submit an updated form FDA 356h to reflect reliance on only the Cerebyx and Carnexiv NDAs.
2. Your June 28, 2019, resubmission included Paragraph IV certifications with respect to the following U.S. Patents Nos. listed under Carnexiv NDA 206030: 7,635,773 (the '773 patent); 8,410,077 (the '077 patent); 9,493,582 (the '582 patent); and 9,750,822 (the '822 patent). Under 21 CFR 314.52(a), you are required to send notice to the NDA holder and each patent owner for which you submitted a Paragraph IV certification, and 21 CFR 314.52(e) requires that you provide documentation of the date of receipt of such notice. The U.S. Patent and Trademark Office (USPTO) identifies Cydex Pharmaceuticals as the patent owner for the '773, '077, '582, and '822 patents. You must send notice of Paragraph IV certification and submit documentation of the date of receipt of such notice by Cydex Pharmaceuticals.
3. On September 23, 2019, you submitted two Domestic Return Receipts for deliveries to Lundbeck Pharmaceuticals, application owner of Carnexiv NDA 206030, as documentation of receipt of Paragraph IV notification. However, the

receipts do not indicate the date of delivery (i.e., in Field C of PS Form 3811). Please submit documentation that clearly shows the delivery date to Lundbeck.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate, including regulatory issues that could potentially impact the labeling. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information¹ and Pregnancy and Lactation Labeling Final Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.³

CARTON AND CONTAINER LABELING

Upon resubmission of your application, submit draft carton and container labeling revised as follows:

(b) (4)

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

² <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

³ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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

PROPRIETARY NAME

Please refer to correspondence dated, August 27, 2019, which addresses the proposed proprietary name, Sesquient. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile.
- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Heather Bullock, Regulatory Project Manager, at (301) 796-1126 or by email at Heather.Bullock@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Acting Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

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/

NICHOLAS A KOZAUER
12/20/2019 02:35:46 PM



NDA 210864

COMPLETE RESPONSE

Sedor Pharmaceuticals, LLC
Attention: Rick Lampe
Director of Regulatory Affairs & Quality Assurance
1800 East Lancaster Avenue, Suite N
Paoli, PA 19301

Dear Mr. Lampe:

Please refer to your New Drug Application (NDA) dated and received May 22, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sesquient (fosphenytoin sodium) injection, 100 mg and 500 mg phenytoin sodium equivalents/mL.

We also acknowledge receipt of your amendment dated March 14, 2019, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Product Quality

1. The proposed prescribing information indicates that the drug product can be diluted in either 5% dextrose or 0.9% saline to a concentration ranging from 1.5 mg phenytoin equivalents (PE)/mL to 25 mg PE/mL.
 - a. The compatibility study was performed at a concentration of 7.5 mg fosphenytoin sodium/mL (5 mg PE/mL) and 15 mg fosphenytoin sodium /mL (10 mg PE/mL). Provide data demonstrating that the drug product is stable at concentrations of 1.5 mg PE/mL and 25 mg PE/mL.
 - b. The compatibility study was only performed using 0.9% sodium chloride. Provide data demonstrating that the drug product is stable in 5% dextrose. Ensure that data include information for 1.5 mg PE/mL and 25 mg PE/mL concentrations.
 - c. Provide a validation package for the method used to determine assay and impurities for the compatibility study.

2. In a response to an information request dated November 16, 2018, you indicated that the assay, identification, and impurity method was originally validated in 2007. Additionally, you stated that the method was not validated specifically for the related substances. This is not acceptable as the accuracy of the results provided to date cannot be assured.

Provide data demonstrating that the method is validated ensuring that impurities remain below the proposed specifications.

As the impurity method has not been adequately validated at this time, the shelf-life for the drug product cannot be determined.

3. We could not locate in-process control testing results for all manufacturing stages for your registration batches in Module 3.2.P.3.4. We recommend that you submit the results in a tabular format. If you have submitted this information earlier, please indicate its exact location.
4. Describe the risk mitigation strategies in your manufacturing process to control the presence of (b) (4) particles (b) (4) in the drug product.

Clinical

Lack of Adequate Information to Support the Safety of Captisol

Although we note that there are some relevant instances of Captisol exposure (infusion rate and total dose) in the Drug Master File (DMF) for Captisol and in the published literature, none were sufficient in all elements of infusion rate, total dose, and detail of safety information to provide adequate support for your proposed product indications. Please note that if you elect to address this deficiency through reliance on FDA's finding of safety for a listed drug or drugs that include Captisol as an excipient, you should identify the listed drug or drugs in accordance with the Agency's regulations at 21 CFR 314.54. The regulatory requirements for a 505(b)(2) application apply to each listed drug on which the application relies and include but are not limited to: 1) providing an adequate bridge to establish that reliance on the listed drug is scientifically appropriate; and 2) providing an appropriate patent certification or statement. Please note that if you elect to provide a paragraph IV certification (21 CFR 314.50(i)(1)(i)(A)(4)) with respect to any relevant patent that claims a listed drug that you choose to rely upon, the certification is to be accompanied by a statement that you will comply with the requirements under § 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under § 314.52(c) with respect to the content of the notice.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing](#)

[Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

CARTON AND CONTAINER LABELING

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(b) (4)



PROPRIETARY NAME

Please refer to correspondence dated, August 16, 2018, which addresses the proposed proprietary name, Sesquient. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
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 4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
 6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
 7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENT

We have the following comment/recommendation that is not an approvability issue:

Product Quality

As noted in our information requests from June 22, 2018, our discussion in the meeting from July 6, 2017, our response to Question 9 of the Type C Meeting dated June 3, 2016, and our response to Question 1 of the Pre-IND meeting dated September 20, 2006, the proposed product does not comply with the USP Monograph for Fosphenytoin Sodium Injection. As previously advised, we encourage you to contact USP with respect to possible revisions to the current monograph that would enable compliance for your product. Revisions are needed for acceptance criteria for both pH and phenytoin impurity limits. Please refer to the following USP website for information regarding guidelines for submitting requests for

revision to the USP-NF through the pending monograph process (http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/pendingStandards/2015-06-01-pending-monograph-guideline.pdf).

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

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You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Heather Bullock, Regulatory Project Manager, at (301) 796-1126 or by email at Heather.Bullock@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/

ERIC P BASTINGS
03/22/2019 12:28:30 PM