CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218879Orig1s000

OTHER ACTION LETTERS

NDA 218879

COMPLETE RESPONSE

OWP Pharmaceuticals, Inc.
Attention: Paul Sudhakar
Director of Scientific Affairs
8827 Long St.
Lenexa, KS 66215

Dear Paul Sudhakar:

Please refer to your new drug application (NDA) dated March 1, 2024, received March 4, 2024, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Subvenite (lamotrigine) oral suspension.

We also acknowledge receipt of your amendment dated November 27, 2024, 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. We acknowledge your response in eCTD 0016 that included the method validation protocol, but your response did not include the report for the analytical method validation of the extractable/leachable studies. We are unable to assess the adequacy of the extractable/leachables studies without adequately validated analytical methods.

   Information Needed to Resolve the Deficiency: Provide the analytical method validation report.

2. The extractables study was repeated under 9 hours of refluxing conditions per your response in eCTD 0020. However, it was stated in the report that the GCMS analysis data was to be “provided in the next report revision.” This is not acceptable because the extractables study is incomplete and does not adequately demonstrate the extractables profile for the proposed drug product.

   Information Needed to Resolve the Deficiency: Provide a complete extractables study that includes GCMS analysis data.

3. We acknowledge your response to our Information Request to provide in-use stability studies, indicating that you will provide these studies once they were completed. These studies are necessary to assess product quality once the proposed drug product is opened and set aside for a period of time. However, these studies were not provided.

   Information Needed to Resolve the Deficiency: Provide the in-use stability studies based on the protocol provided in eCTD 0009 and the commitment to assess sedimentation as part of the in-use study in eCTD 0016.

4. The proposed stability specification of lamotrigine related compound D is listed as no more than (NMT) (b) (4)%. It was justified in eCTD 0009 with reference to the USP monograph for lamotrigine tablets. This justification is not adequate, as there is no specification for lamotrigine related compound D in the USP monograph for lamotrigine tablets, and the proposed specification limit is above ICH qualification thresholds.

   Information Needed to Resolve the Deficiency: Revise the specification for lamotrigine-related compound D to be NMT 0.2%.

Biopharmaceutics

1. We acknowledge that you have provided additional information regarding the dissolution method. However, the provided information is not satisfactory. Refer to the following comments for the additional information we recommend you provide to potentially address this deficiency.

   a. We acknowledge that you have revised the dissolution method by changing the dissolution media (b) (4). Note that (b) (4) is not recommended as dissolution medium because it lacks buffering capacity. Therefore, an aqueous dissolution medium with buffering capacity within the physiologic pH range is recommended.

   b. The solubility data show that lamotrigine is poorly soluble within the physiologic pH range of 1.2 to 6.8. However, the drug product seems to exhibit rapid to very rapid dissolution. Understanding this discrepancy may aid in the development of a dissolution method that is suitable for the proposed drug product. Note that for oral suspension drug products, you should include investigation of lower paddle speeds, e.g., 25, 30, 35, and 40 rpm, in your method development. Additionally, each sample tested should be taken from a different bottle and the same volume should be administered according to the labeling dosing instructions. The selection of the test conditions/parameters needs to be justified with supporting information and data.

c. We recommend you explore the discriminating ability of the proposed dissolution method/test conditions and submit these data. In general, the tests conducted to demonstrate the discriminating ability should compare the dissolution profiles of the reference (target) batch and batches that are intentionally manufactured with meaningful variations in the most relevant critical material attributes, critical formulation variables, and critical process parameters (i.e., ± 10-20% change to the specification-ranges of these variables). A discriminating method (along with the selected acceptance criterion) should be able to reject batches that fail similarity testing. In addition, if available, submit data showing that the selected dissolution method (along with the selected dissolution acceptance criterion) can reject batches that are not bioequivalent to the reference batch (i.e., the biobatch).

d. You should generate new dissolution profile data for clinical/registration batches using the revised dissolution method and propose an appropriate acceptance criterion based on the newly generated profile data and taking into consideration results of the method's discriminating ability.

e. Note that comparison of the dissolution profile of the proposed product to the listed drug is not needed.

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 Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] 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

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

The following are draft carton and container labeling comments which should be addressed in any subsequent resubmission:

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the format for the expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used, or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See the guidance document, *Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers* (June 2021).
2.	The placeholder for the lot number is missing.	Lot number statement is required on the immediate container AND carton labeling when there is	Add the placeholder for the lot number to the container label and the carton labeling in

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		sufficient space, per 21 CFR 201.10(i)(1).	accordance with 21 CFR 201.10(i)(1). See also recommendation below regarding the product identifier for the carton labeling.
3.	The recommended dosage statement can be improved.	This statement may be revised to ensure consistency with the terminology in the prescribing information.	Revise the dosage statement (b) (4) to read "Recommended Dosage: See prescribing information."
4.	The discard statement "Discard any unused product remaining after ninety (90) days of first opening the bottle" lacks prominence.	Lack of prominence may result in overlooked information, which may lead to risk of administration of degraded drug product.	Consider increasing the prominence of the discard statement by using bold font or by other means. Also refer to comment #5 below.
5.	As currently presented, (b) (4) "Discard After", for the beyond use date. (b) (4) Discard After: ____/____/____	(b) (4) This may lead to risk of administration of deteriorated drug product or usable unused product being discarded before 90 days.	We recommend allocating only one space to write the beyond use date (i.e., "Discard After" date). Also, consider relocating the statement "Discard any unused product remaining after ninety (90) days of first opening" to appear directly above the "Discard After" date (see comment # 4 directly above). For example: **Discard any unused product remaining after ninety (90) days of first opening.** Discard After __/__/__
6.	The overall font type, style, and kerning for the strength statement "10 mg/mL" is difficult to read as shown below:	Narrow, light typeface font with tight kerning, or spacing between characters, may impact the readability of the strength statement.	To improve readability, we recommend adjusting the font type/style (e.g., consider a less narrow and/or more bold option) and improving the kerning in the strength

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			statement so that the strength fills up more of the (b) (4) box. For example: 
7.	The established name "lamotrigine USP" is not at least half the size of the proprietary name. Overall, the entire established name and dosage form statement "(lamotrigine USP) Oral Suspension" lacks sufficient prominence.	We refer you to 21 CFR 201.10(g)(2), which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name, and the established name shall have a prominence commensurate with the prominence with which such proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.	Increase the prominence (i.e., increase the font size, use bold font) of the established name and dosage form to improve readability and to be in alignment with 21 CFR 201.10(g)(2).
8.	As currently presented, the finished dosage form statement (b) (4) directly underneath the strength statement is not in alignment with USP requirements [General chapter <1121> nomenclature] for this type of pharmaceutical dosage form.	The dosage form for this product is "oral suspension". Additionally, the correct dosage form statement "Oral Suspension" is already present on the PDP of the container label and carton labeling.	We recommend removing the incorrect duplicate dosage form statement (b) (4)
9.	The net quantity statement (b) (4)	Inconsistent net quantity information can lead to	Clarify which net quantity statement (b) (4) or 8 oz

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	on the container and carton labeling is inconsistent with the quantity statement (i.e., 8 oz (240 mL)) in Section 16 of the prescribing information (PI).	confusion during ordering and distribution of the drug product.	(240 mL)) is correct for your proposed product. Revise the net quantity statement to accurately reflect the total volume per bottle consistently across all labels and labeling.
10.	The first temperature numerical of each temperature range is missing the Celsius or Fahrenheit symbol.	The storage statement should be clearly stated to prevent incorrect storage which may lead to deteriorated drug medication errors.	Revise the storage statement to read “Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].”
11.	The storage statement “DO NOT FREEZE” is presented in all capital letters in bold font.	This competes in prominence with other important information on the side panel.	We recommend de-bolding the “DO NOT FREEZE” statement and presenting the text in mixed-case lettering. For example, “Do Not Freeze”.
12.	The discard statement “Discard any unused product remaining after ninety (90) days of first opening the bottle” lacks prominence.	Lack of prominence may result in overlooked information which may lead to risk of administration of degraded drug product.	Consider increasing the prominence of the discard statement by using bold font or by other means.
13.	As currently presented, the (b) (4) colored graphics, OWP logos, and (b) (4) images compete in prominence with critical and/or important information on the container label and carton labeling.	Per 21 CFR 201.15, critical product information such as the proprietary, established name, strength, and dosage form should appear as the most prominent information on the principal display panel. Specifically, we have the following concerns: • The (b) (4) colored graphic in front of the proprietary may detract from the readability of	Therefore, we recommend the following: • Consider relocating and/or decreasing the prominence of the graphic in front of the proprietary name on the container label and carton labeling. • Consider decreasing the prominence of the graphic on the side panel of the carton labeling such that it does not compete in prominence with important information.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		the proprietary name and established name. • Additionally, the large (b) (4) colored graphic on the side panel of the carton labeling, the OWP logos, and the (b) (4) images may distract the reader from critical information and other important information, such as the storage information and discard statements.	• Consider decreasing the prominence of the OWP name and logo on the container label and carton labeling such that it does not compete in prominence with important information. • Consider decreasing the size of the (b) (4) graphic on the carton labeling such that it does not compete in prominence with critical information and other important information.
Container Label			
1.	The (b) (4) statement on the container label is not necessary and is promotional in tone.	Per 21 CFR 201.56(a)(2), the labeling must be informative and accurate and not promotional in tone.	We recommend removing (b) (4)
Carton Labeling			
1.	The product identifier is missing.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See the guidance document, *Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers* (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder to the carton labeling.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		machine-readable (2D data matrix barcode) format.	
2.	As currently presented, the statement [redacted] is inconsistent with the statement on the container label (i.e., "SHAKE WELL BEFORE EACH USE").	Inconsistent preparation instructions may lead to confusion.	If a specific time requirement for shaking has not been established, we recommend revising the "shake" statement to read "Shake Well Before Each Use" to be consistent with the container label.
3.	The same background color [redacted] is used to highlight the net quantity statement and the strength statement (i.e., 10 mg/mL).	Using the same color to highlight the strength statement and net quantity statement minimizes the difference between them and may lead to confusion.	We recommend removing the [redacted]-colored box highlighting the net quantity statement on the carton labeling.

FACILITY INSPECTIONS

The drug substance manufacturing facility, [redacted], proposed to support the application is not operational. A satisfactory inspection may be required before this application may be approved. As part of your full response to this Complete Response letter, confirm that this facility is ready for inspection. Note that the application cannot be approved if any proposed facility for the commercial manufacturing is not acceptable for the proposed function on the action date.

PROPRIETARY NAME

Refer to correspondence dated, June 4, 2024, which addresses the proposed proprietary name, Subvenite. This name was found conditionally acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

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 dropouts from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject 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 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 product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Kelly Ross, Regulatory Health Project Manager via email at Kelly.Ross@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Paul R. Lee, MD, PhD, MA
Director (Acting)
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/

PAUL R LEE
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