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RESEARCH**

APPLICATION NUMBER:

211321Orig1s000

OTHER ACTION LETTERS



NDA 211321

COMPLETE RESPONSE

Proximagen, LLC
Attention: Encarnacion Suarez, PharmD
Director, Global Regulatory Affairs
505 Waterford Park, Highway 169 North, Suite 850
Plymouth, MN 55441

Dear Dr. Suarez:

Please refer to your New Drug Application (NDA) dated May 27, 2018, received May 29, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Nayzilam (midazolam) nasal spray 5 mg/0.5 mL.

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.

QUALITY SYSTEM

We refer to our November 13, 2018, letter which identified Quality System deficiencies and requested additional information. The deficiencies, identified in our November 13, 2018, letter, assumed that Proximagen was the applicant for NDA 211321, and that (b) (4) was the contract manufacturer. As such, the Quality System deficiencies were limited to these firms.

Based on your, March 8, 2019, Response to the March 5, 2019, FDA-483 that FDA issued to you, it appears that UCBBioPharma SPRL (UCB) has purchased this NDA and is integrally involved in several aspects of the Quality System at your firm. You will need to update your responses to FDA's November 8, 2019, Quality System deficiencies to additionally identify how the manufacturer UCB integrates into the Quality System established at your firm.

1. You have not adequately addressed the requirements for 21 CFR 820.20, Management Responsibility. Please describe the specific management control responsibilities at each facility associated with the medical device constituent of this combination product. To date, we are aware that the only facilities with potential management control responsibilities are Proximagen, (b) (4), and UCB. Please provide a summary of how your firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product.

2. You have not adequately addressed the requirements for 21 CFR 820.30, Design Controls. Please explain the extent to which UCB is involved in the design control process. You will need to specifically provide the procedures established at UCB to demonstrate how design controls are implemented at UCB; this includes how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are fulfilled.
3. You have not adequately addressed the requirements for 21 CFR 820.50, Purchasing Controls. Please provide a summary of the procedure(s) at UCB for purchasing controls. The summary should delineate the purchasing control responsibilities at Proximagen, (b) (4), and UCB:
 - a. Describe supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers.
 - b. Define how the records of acceptable suppliers will be maintained and how your firm addresses the purchasing data approval process.
 - c. Explain how your firm will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

Please explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Please provide a description of how your firm applies the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).

4. You have not adequately addressed the requirement for 21 CFR 820.100, Corrective and Preventive Actions. Specifically, it appears that UCB is integrated into the overall Quality System at your firm. Please summarize the procedure(s) for your firm's Corrective and Preventive Action (CAPA) System, and specifically delineate how each facility is responsible for your CAPA system. The CAPA system should require:
 - a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
 - b. Investigation of nonconformities and their causes;
 - c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and
 - d. Verification or validation of the actions taken.
5. Please provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This diagram should specifically identify which facility is responsible for each step in your manufacturing process. This information should display the important aspects of the production process.

6. Please explain how UCB will integrate into the processes for controlling the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. You will need to specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. You will also need to provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. The version of the Prescribing Information, Medication Guide, and Instructions for Use appended to this letter should be included in your resubmission. If you include any proposed revisions to the labeling, in your resubmission in response to this letter, use the versions appended to this letter as the base documents with any revisions shown as tracked changes.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling based on your submissions dated March 21, 2019, and March 27, 2019.

PROPRIETARY NAME

Please refer to correspondence dated, August 23, 2018, which addresses the proposed proprietary name, Nayzilam. 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.

FACILITY INSPECTIONS

During a recent inspection of the UCB manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

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 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, call Harold Sano, Regulatory Project Manager, at (301) 796-2429.

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

ENCLOSURES:

Content of Labeling
Medication Guide
Instructions for Use

27 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/

ERIC P BASTINGS
03/29/2019 05:57:13 PM