NDA 216834

NDA APPROVAL

UCB, Inc.
Attention: Robert McNeill, PhD, RAC
Regulatory Science Lead
400 Paramount Parkway, Suite 200
Morrisville, NC 27560

Dear Dr. McNeill:

Please refer to your new drug application (NDA) dated August 31, 2022, received August 31, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zilbrysq (zilucoplan) injection.

We acknowledge receipt of your major amendment dated August 29, 2023, which extended the goal date by three months.

This NDA provides for the use of Zilbrysq (zilucoplan) injection for the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on August 29, 2023, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 216834**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Zilbrysq (zilucoplan) injection shall be 36 months from the date of manufacture when stored at 2°C to 8°C.

ADVISORY COMMITTEE

Your application for Zilbrysq was not referred to an FDA advisory committee because the application did not raise significant public health questions regarding the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an

unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Zilbrysq (zilucoplan) during pregnancy.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

4487-1 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to zilucoplan during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

The timetable you submitted on July 13, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	05/2024
Final Protocol Submission:	03/2025
Interim Study Report:	03/2026
	03/2027
	03/2028
	03/2029
	03/2030
	03/2031
	03/2032
	03/2033
	03/2034
Study Completion:	03/2035
Final Report Submission:	03/2036

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of the potential presence of zilucoplan in human breast milk resulting in effects on the breastfed infant.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4487-2 Perform a lactation trial (milk only) in lactating women who have received therapeutic doses of zilucoplan using a validated assay to assess concentrations of zilucoplan in breast milk and the effects on the breastfed infant as applicable.

The timetable you submitted on July 13, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	04/2024
Final Protocol Submission:	02/2025
Study Completion:	07/2026
Final Report Submission:	12/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 134340 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Food Drug Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Zilbrysq (zilucoplan) to ensure the benefits of the drug outweigh the risk of serious meningococcal infections.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that Zilbrysq (zilucoplan) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of serious meningococcal infections listed in the labeling of the drug.

Your REMS includes the following elements to mitigate this risk:

- Healthcare providers (HCPs) have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require: pharmacies that dispense the drug be specially certified, and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on August 31, 2022, amended and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Zilbrysq (zilucoplan) into interstate commerce.

The REMS assessment plan must include, but is not limited to, the following:

For each metric, the two previous, current, and cumulative reporting periods (where applicable) will be provided unless otherwise noted.

Program Outreach and Communication

1. REMS communication activities

Activities related to the distribution of the REMS Letters (annual vaccination reminders) to prescribing HCPs will be assessed, and the following metrics will be reported:

   a. Sources for the distribution lists for prescribing HCPs
   b. Number of prescribing HCPs targeted
   c. The number of REMS Letters (annual vaccination reminders) sent by date and method of distribution
   d. The number and percentage of REMS Letters (annual vaccination reminders) sent via:
      i. Email that were successfully delivered, opened, and unopened
      ii. Fax that were successfully delivered

Program Implementation and Operations

2. REMS implementation (for the first REMS Assessment only)
   a. Date of Zilbrysq REMS launch
   b. Date when the Zilbrysq REMS website became live and fully operational
   c. Date when HCPs and pharmacies could become certified/enrolled in the REMS
   d. Date when distributors/wholesalers or entities able to distribute were authorized to distribute the drug (i.e., first order placed)
   e. Date when the REMS Coordinating Center was established and fully operational
   f. Date of first commercial distribution of Zilbrysq
3. REMS Certification and Enrollment Statistics
   a. Health Care Provider (HCP) certification
      i. The number of HCPs certified: total, newly certified, and active (i.e., prescribed Zilbrysq at least once during the reporting period) stratified by credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Advanced Practice Registered Nurse, Physician Assistant, Other), medical

specialty (e.g., Neurology, Other), and geographic region (as defined by US Census)

ii. Method of HCP certification (e.g., fax, online)

iii. The number of HCPs who prescribed but were unable to become certified, accompanied by a summary of the reason(s) why they were unable to be certified

b. Pharmacy certification

i. The number and identity of each outpatient pharmacy certified: total, newly enrolled, and active (i.e., dispensed Zilbrysq at least once during the reporting period), stratified by geographic region (as defined by US Census)

ii. Method of pharmacy certification (e.g., fax, online)

iii. The number of pharmacies that dispensed Zilbrysq but were unable to become certified, accompanied by a summary of the reason(s) why they were unable to become certified

c. Wholesalers/Distributors and other entities that distribute Zilbrysq

i. The number and identity of each wholesaler/distributor or entity authorized to distribute: total, newly authorized and active (distributed Zilbrysq at least once during the reporting period)

4. Zilbrysq Utilization Data

a. The number of Zilbrysq shipments sent to pharmacies, overall, and stratified by quantity per shipment

b. For certified pharmacy, the number of prescriptions dispensed stratified by:

i. Prescriber specialty, degree/credentials, and geographic region

ii. Patient demographics (e.g., age, gender), and geographic region (as defined by US Census)

iii. Whether the prescription was new or a refill

c. The number of unique patients who received Zilbrysq stratified by age, gender, and geographic region (as defined by US Census)

d. Percentage (%) of Zilbrysq dispenses corresponding to prescriptions written by REMS certified HCPs

e. The number of prescriptions not dispensed, accompanied by a listing and summary of all reasons for not dispensing the prescription (e.g., HCP not certified, REMS related issue)

5. REMS Compliance

a. A summary report of noncompliance status, and the status of corrective and preventive action (CAPA) plans including, but not limited to:

i. A copy of the noncompliance plan, including the criteria for the determination of noncompliance for prescribers and pharmacies, action(s) taken to address all instances of noncompliance, and which events will lead to suspension or decertification from the REMS

ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, the following information will be reported:

   a) The unique identification (ID) of the stakeholder(s) associated with the noncompliance event to enable tracking over time

   b) The source of the noncompliance data

   c) The results of root cause analysis

   d) The action(s) taken in response to noncompliance

iii. The number and percentage of prescribers who prescribed Zilbrysq but were not certified as identified by the certified pharmacy

iv. The specific reasons why prescribers were not certified at the time of prescribing (i.e., emergency use, etc.), and whether these prescribers subsequently became certified

v. The number and percentage of drug distributions to pharmacies that are not certified

vi. The specific reasons for the drug distributions to pharmacies that are not certified

vii. The number of pharmacies who became decertified, accompanied by a summary of reasons for decertification

b. Audits: Summary of audit activities including but not limited to:

i. A copy of the audit plan used for each audited stakeholder (i.e., pharmacies, REMS call center, and wholesalers, distributors, and other entities that distribute Zilbrysq)

ii. The number of audits expected, and the number of audits performed for each stakeholder

iii. The number and category of observations noted, stratified by category

iv. A unique ID for each stakeholder that had observations to track observations by stakeholder over time

v. Documentation of completion of training for relevant staff

vi. A summary report of documented processes and procedures for complying with the REMS requirements including how certified pharmacies obtain patient vaccination status from HCPs

vii. Verification that at each audited pharmacy location, a designated Authorized Representative is certified and certification is up to date

viii. Describe any corrective actions taken for any noncompliance (audit observation) identified during audits as well as any preventative measures that were developed from identifying these noncompliance events

a) For stakeholders with observations noted within the audit report, provide the number that successfully completed a CAPA plan by the due date

b) For any that did not complete the CAPA plan by the due date, describe additional actions taken

6. REMS Infrastructure and Performance

a. REMS Website

i. The number of visits and unique visits to the REMS website

ii. The number of REMS materials downloaded or printed for each REMS material

b. REMS Coordinating Center Report

i. The number of contacts by stakeholder type (patient/caregiver, HCP, etc.)

ii. A table summarizing the reasons for calls (e.g., enrollment question) by stakeholder type

iii. If the reason for the call indicates a complaint, details on the nature of the complaint and whether they indicate potential REMS burden or patient access issues

iv. A summary report of corrective actions resulting from issues identified

Safe Use Behaviors

7. Safe Use Behaviors

a. Information captured by pharmacies regarding the number and percentage of patients who were vaccinated against *Neisseria meningitidis (*serogroups A, C, W, Y, and B vaccines). The following information will be documented:

i. The date of first vaccine administration for each serogroup

ii. The number of days between vaccination and initiation of therapy with Zilbrysq (if available)

iii. Status and date of second vaccine doses and booster doses for MenACWY and MenB serogroup vaccines (if available)

iv. The date when Zilbrysq was first dispensed

v. Whether the patient received antibacterial drug prophylaxis, and timing of antibacterial drug prophylaxis in relation to the dosing of Zilbrysq (if available)

vi. If any of the above information is missing, the reasons why this information is missing such as:

a) HCP records do not include this information

b) HCP declined to provide information

c) HCP did not respond to Pharmacy queries

b. The number and percentage of new patients treated with Zilbrysq who completed or were up to date with meningococcal vaccinations (MenACWY and MenB) as per the most current Advisory Committee on Immunization Practices (ACIP) recommendations

c. The number and percentage of patients who did not receive meningococcal vaccinations (MenACWY and MenB) in accordance with the current ACIP recommendations or given antibacterial drug prophylaxis if needed, prior to initiating treatment with Zilbrysq

Include a narrative describing the vaccines that were not administered (i.e., *Neisseria meningitidis* serogroups)

d. The number and percentage of patients who received the first dose of meningococcal vaccines (MenACWY and MenB) and antibacterial drug prophylaxis if needed before the first dispense

e. For patients who were not initially up to date with meningococcal vaccines when starting treatment, report the number and percentage who, up to 6 months after the first dose:

i. Completed meningococcal vaccines (received both MenACWY and MenB)

ii. Did not complete meningococcal vaccines but were receiving antibacterial drug prophylaxis

iii. Vaccination status was unknown after completed follow-up attempts

Health Outcomes and/or Surrogates of Health Outcomes

8. Summary of cases of meningococcal infections in patients receiving Zilbrysq

a. For US cases of meningococcal infections, cases are summarized as follows:

i. In the most recent Periodic Safety Update Report (PSUR) submitted to the Zilbrysq NDA with reference to the PSUR corresponding with the reporting interval

ii. A cumulative listing of all cases of meningococcal infections from approval to include cases identified during the current reporting period

b. For each US case of meningococcal infection, the following information, if available, will be provided:

i. MedWatch or other case report number

ii. Date of event and date of report to FDA

iii. Patient age, race, and gender

iv. Indication for Zilbrysq treatment

v. Meningococcal vaccination status:

   a) Date of vaccine(s) (i.e., all of the meningococcal vaccines doses (ACWY and MenB) that a patient received including the first vaccine dose, second vaccine dose, and booster doses)

   b) Name of vaccine(s)

   c) Timing in relation to Zilbrysq (i.e., the dates or duration that a patient received Zilbrysq in relation to the meningococcal vaccine(s))

   d) ACIP compliance and antibacterial drug prophylaxis status

      1) Antibacterial drug prophylaxis regimen

      2) Timing (i.e., include the dates or duration that a patient received Zilbrysq in relation to antibacterial drug prophylaxis)

   e) Clinical course

      1) Outcome and causative meningococcal serogroup

      2) Source of the vaccine information when available. For information that is not available (listed as “unk” or “unknown”) the number and type (patient, prescriber, etc.) of outreach attempts made to obtain the information for each case. Also, if the information is not available, a narrative is presented explaining why the information is unknown (“unk”) or unavailable for each reported case

vi. Whether or not the patient was administered antibacterial drug prophylaxis and if so:

   a) The specific antibacterial drug, antibacterial drug regimen (dose/frequency), and routes of administration

   b) The timing of the course of the antibacterial drug prophylaxis in relation to Zilbrysq treatment

vii. Summary of the clinical course and the outcome; specifically report whether the patient:

   a) Was admitted to an intensive care unit

   b) Experienced any organ system failure, such as (but not limited to) requiring mechanical ventilation or medication (vasopressors) to support blood pressure

   c) Died

viii. The length of time between onset of symptoms and when the patient presented for medical evaluation (if available).

ix. Causative meningococcal serogroups

x. Whether the Patient Safety Card was presented during the process of the patient seeking treatment

c. For each non-US case of meningococcal infection, the following information, as available, will be provided:

i. Case report number

ii. Patient age and gender

iii. Indication for Zilbrysq treatment

iv. Meningococcal vaccination status if known

v. Outcome

vi. If associated with any clinical trials

9. Meningococcal Infections Rate (per year and cumulatively)

a. Among patients who received Zilbrysq in the US and worldwide:

i. The number of reported cases of meningococcal infections per 100,000 patient-years of postmarketing exposure to Zilbrysq; reporting rate will be summarized cumulatively since the approval of Zilbrysq and stratified by year and relevant age subgroups (≤ 18 years, 19-55 years, and >55 years).

Knowledge

10. Provide stakeholder surveys for prescribing HCPs and patients (beginning with the 1-year assessment report and annually thereafter)

a. Assessment of prescribing HCPs' and patients' awareness regarding:

i. Patients are vaccinated against meningococcal infections caused by *Neisseria meningitidis* serogroups A, C, W, and Y (MenACWY) and serogroup B (MenB) prior to starting therapy according to the current Advisory Committee on Immunization Practices recommendations (ACIP) and receive antibacterial drug prophylaxis if needed

ii. The early signs and symptoms of meningococcal infections

iii. The need for immediate medical evaluation

Overall Assessment of REMS Effectiveness

11. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or

methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

i. Submit your proposed audit plan and non-compliance plan for FDA review within 60 days of this letter.

ii. Submit your proposed protocol for the knowledge survey(s) for FDA review within 90 days of this letter.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 216834 REMS ASSESSMENT METHODOLOGY**
> **(**insert concise description of content in bold capital letters, e.g., **ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 216834 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 216834/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 216834/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 216834/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 216834/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 216834

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For additional information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-*

Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.[5]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for serious events related to pancreatitis and other pancreatic adverse events, and for infection, including meningococcal infection and opportunistic infection. Include analyses of individual events as well as comprehensive summaries and analyses of these events, including incidence, quarterly as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. Include analyses of the events by age and sex. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, such as meningococcal vaccination history and antibiotic use in the case of infections, along with extent of exposure to Zilbrysq and most recent exposure to Zilbrysq, concomitant therapies, treatment given for the event, and outcome.

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[8].

If you have any questions, contact Michael Matthews, Regulatory Project Manager, via email at Michael.Matthews@fda.hhs.gov or phone at (301) 796-3047.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- REMS

[8] https://www.uspnf.com/

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/

TERESA J BURACCHIO
10/17/2023 11:13:55 AM