NDA 216834/S-08
NDA 216834/S-09

SUPPLEMENT 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 supplemental new drug applications (sNDAs) dated and received August 29, 2024, and September 3, 3024, respectively, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zilbrysq (zilucoplan) injection.

These Prior Approval sNDAs provide for revision of information regarding serious meningococcal infections to align the Zilbrysq labeling with the labeling for other complement inhibitors and for proposed modifications to the approved Zilbrysq risk evaluation and mitigation strategy (REMS). These supplements are in response to our August 2, 2024, Prior Approval Supplement Request letter. Revisions were made in the following sections of labeling, as well as the Medication Guide:

BOXED WARNING
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Vaccination and Prophylaxis for Meningococcal Infection
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Serious Meningococcal Infections
5.2 ZILBRYSQ REMS
5.3 Other Infections
17 PATIENT COUNSELING INFORMATION

APPROVAL & LABELING

We have completed our review of these applications, as amended and they are 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), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, 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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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

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 none of these criteria apply to your supplemental applications, you are exempt from this requirement.

[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.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Zilbrysq was originally approved on October 17, 2023, and the most recent REMS modification was approved on January 16, 2024. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS include the following:

- REMS Document
  - Changes to the REMS goal to remove mention of specific meningococcal vaccine types to align with labeling with respect to current Advisory Committee on Immunization Practices (ACIP) recommendations for patients receiving complement inhibitors.
  - Changes to the target audience for the REMS Letter: Vaccination reminder to REMS certified prescribers, to clarify that the letter is sent to all prescribers certified in the REMS.
  - Changes to the timing of audits for certified pharmacies.
- REMS materials
  - Changes to align with labeling, and to improve clarity and formatting.

Your proposed modified REMS, submitted on September 3, 2024, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on October 17, 2023.

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

iii. Whether the prescription was new or a refill reported as a total across all pharmacies

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

d. The number and 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 identified, associated corrective and preventative action (CAPA) plan, and the status of CAPA plans including, but not limited to:

i. A copy of the noncompliance plan, including the criteria for the determination of noncompliance for prescribers pharmacies, and wholesalers/distributors, and other entities that distribute Zilbrysq, action(s) taken to address all cases of noncompliance, and which

events will lead to suspension or decertification, if applicable, 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, report the following information:

a) The unique identification (ID) of the participant(s) associated with the noncompliance event or deviation 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

a) 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

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

a) The specific reasons for the drug distributions to pharmacies that are not certified

v. 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 participant (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 participant

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

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

v. Documentation of completion of training for relevant staff (those involved in the distribution or dispensing of Zilbrysq)

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

a) As part of reviewing the processes and procedures, review the methods utilized to determine whether patients received meningococcal vaccines in accordance with the most current Advisory Committee on Immunization Practice (ACIP) recommendations for patients receiving a complement inhibitor.

vii. Verification that at each audited participant's site, the designated Authorized Representative is up to date. If the Authorized Representative changes, include the number of new Authorized Representatives and verification of each site's recertification

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 those with deficiencies noted, report 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 participant type (patient/caregiver, HCP, pharmacy, etc.)

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

iii. Details on any complaint(s) received and whether they indicate potential REMS burden or patient access issues

iv. Details on any corrective actions implemented due to identified issues.

Safe Use Behaviors

7. Safe Use Behaviors

Determination of patients' vaccination and antibacterial drug prophylaxis compliance is made using data collected via the certified pharmacies documenting the patients' vaccination status and antibacterial drug prophylaxis status.

a. Methods used to determine whether or not patients received meningococcal vaccinations in accordance with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients receiving a complement inhibitor. Include vaccine serogroup, dosing (i.e., first vaccine dose, second vaccine dose, and booster doses), and timing of the vaccinations, when the information is provided.

b. Data on the number and percentage (%) of new patients dispensed Zilbrysq who received at least one meningococcal vaccination(s) prior to first dispense out of the total number of new patients who received Zilbrysq. Of those who received meningococcal vaccination(s), provide the number and percentage who, prior to first dispense:

   i. Received complete primary vaccination(s) series in accordance with the most current ACIP recommendations for meningococcal vaccination in patients receiving a complement inhibitor stratified by vaccine type administered (i.e., serogroups A, C, W, Y, and B).

   ii. Did not receive complete primary vaccination(s) series in accordance with the most current ACIP recommendations for meningococcal vaccination in patients receiving a complement inhibitor stratified by vaccine type administered.

   iii. Did not have all the information necessary for determining compliance of the complete primary vaccination series with the most current ACIP recommendations for meningococcal vaccination in patients receiving a complement inhibitor stratified by vaccine type administered.

c. Data on the number and percentage (%) of new patients dispensed Zilbrysq who did not receive any meningococcal vaccination(s) prior to first dispense out of the total number of patients who received Zilbrysq.

d. Data on whether the patient received antibacterial drug prophylaxis, and a summary analysis of the timing of antibacterial drug prophylaxis in relation to the first dispense of Zilbrysq (if available)

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

i. HCP records do not include this information

ii. HCP declined to provide information

iii. Pharmacy unable to get healthcare provider to respond to queries

f. The number and percentage (%) of new patients dispensed Zilbrysq who received the first dose of meningococcal vaccines (for serogroups A, C, W, Y, and B) and antibacterial drug prophylaxis, if needed, before the first dispense according to the most current ACIP recommendations in patients receiving a complement inhibitor

g. The number and percentage (%) of new patients dispensed Zilbrysq who completed or were up to date with primary series meningococcal vaccinations (serogroups A, C, W, Y, and B) before the first dispense as per the most current ACIP recommendations in patients receiving a complement inhibitor.

h. The number and percentage (%) of new patients dispensed Zilbrysq who, at 6 months after the first dispense, completed or were up to date with the primary series of meningococcal vaccinations (serogroups A, C, W, Y, and B) per the most current ACIP recommendations in patients receiving a complement inhibitor.

i. For patients who were not initially up to date with the primary series of meningococcal vaccines (serogroups A, C, W, Y, and B) before the first dispense or the information was unknown, report the number and percentage who, up to 6 months after the first dispense:

i. Completed primary series of meningococcal vaccines (received A, C, W, Y and B serogroups)

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

iii. Primary series vaccination status was unknown after completed follow-up attempts

j. For new patients dispensed Zilbrysq who at the time of dispense were eligible for meningococcal vaccination (serogroups A, C, W, Y, and B) boosters per the most current ACIP recommendations in patients receiving a complement inhibitor, the number and percentage (%) of patients who received one or more boosters within 6 months of Zilbrysq dispense stratified by vaccination serogroup.

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 New Drug Application (NDA) with a link to that PSUR corresponding with the reporting interval

   ii. Cumulative listing of all US cases of meningococcal infections from approval to the end of 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 sex

   iv. Indication for Zilbrysq treatment

   v. Meningococcal vaccination status:

      a) Date of vaccine(s) (i.e., all of the meningococcal vaccines doses for serogroups A, C, W, Y, and B) 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

      e) 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/duration), and route(s) 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, provide the following information, as available:

i. Case report number

ii. Patient age and sex

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.

Knowledge

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

a. Assess HCPs' and patients' awareness regarding:

i. Patients are vaccinated against meningococcal infections caused by *Neisseria meningitidis* serogroups A, C, W, Y, and B prior to starting therapy according to the current ACIP recommendations for patients receiving a complement inhibitor 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.

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) of the FDCA. 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 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 that 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 REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

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)

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 REVISIONS 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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

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

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

If you have any questions, call Susan Daugherty, Regulatory Project Manager at (301) 796-0878 or email Susan.Daugherty@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Laura Jawidzik, MD
Deputy Director
Division of Neurology 1
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

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

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/

SUSAN B DAUGHERTY
02/28/2025 12:08:21 PM

LAURA A JAWIDZIK
02/28/2025 12:31:28 PM