NDA 209899/S-001

SUPPLEMENT APPROVAL

Celgene International II Sàrl
Attention: Petra Pavlickova, PhD, RAC
Associate Director, Regulatory Affairs
3033 Science Park Road, Suite 300
San Diego, CA 92121

Dear Dr. Pavlickova:

Please refer to your supplemental new drug application (sNDA) dated and received November 30, 2020, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zeposia (ozanimod) capsules.

This Prior Approval supplemental new drug application provides for the use of Zeposia (ozanimod) for the treatment of moderately to severely active ulcerative colitis in adult patients.

APPROVAL & LABELING

We have completed our review of this application. 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 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.

[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.

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).

CARTON AND CONTAINER LABELING

We acknowledge your November 30, 2020, submission containing final printed carton and container labeling.

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 Federal Food, Drug, and Cosmetic Act (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 from the use of Zeposia (Ozanimod) 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 these serious risks.

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

4066-1 An international, prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of females exposed to ZEPOSIA (ozanimod) during pregnancy with women exposed to any other ulcerative colitis therapy during pregnancy and an unexposed comparator population. External disease matched comparators and use of existing disease registries can be considered. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. This study can be conducted as part of the ongoing study under NDA 209899 PMR 3809-3.

The timetable you submitted on May 26, 2021 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2021
Final Protocol Submission:	06/2022
Interim Report #1 Submission:	06/2025
Interim Report #2 Submission:	06/2028
Study Completion:	06/2032
Final Study Report:	06/2033

4066-2 A pregnancy outcomes study using a different study design than provided for in PMR 4066-1 (for example, a retrospective cohort study using claims or electronic medical record data) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in females exposed to ZEPOSIA (ozanimod) during pregnancy compared to an unexposed control population. This study can be conducted as part of the ongoing study under NDA 209899 PMR 3809-4.

The timetable you submitted on May 26, 2021 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2021
Final Protocol Submission:	06/2022
Interim Report #1 Submission:	06/2025
Interim Report #2 Submission:	06/2028
Study Completion:	06/2032
Final Study Report:	06/2033

4066-3 A lactation study (milk only) in lactating women who have received therapeutic doses of ZEPOSIA (ozanimod) using a validated assay to assess concentrations of ZEPOSIA (ozanimod) and its major metabolites in breast milk, and effects on the breastfed infant.

The timetable you submitted on April 28, 2021 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2022
Final Protocol Submission:	09/2022
Study Completion:	09/2024
Final Study Report:	09/2025

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]

Submit the protocol(s) to your IND 115243, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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 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 and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 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

[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.

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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4066-4 A one year, randomized, blinded trial to evaluate the safety, efficacy, and pharmacokinetics of ZEPOSIA (ozanimod) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

The timetable you submitted on April 28, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2021
Trial Completion:	12/2025
Final Study Report:	06/2026

4066-5 A long term extension study to evaluate the long-term safety of ZEPOSIA (ozanimod) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis who participated in postmarketing commitment Study 3. This study can be conducted as part of postmarketing commitment study 4066-4.

The timetable you submitted on April 28, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2021
Trial Completion:	10/2030
Final Study Report:	04/2031

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 115243 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be

prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

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.*[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

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, contact Jay Fajiculay, Regulatory Health Project Manager, at (301) 796-9007 or email at jay.fajiculay@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jessica J. Lee, MD, MMSc
Director
Division of Gastroenterology
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

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

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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/

JESSICA J LEE
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