

NDA 209899

NDA APPROVAL

Celgene Corporation
Penny Ng, DRSc., MBA, RAC
Senior Director, Regulatory Affairs
86 Morris Avenue, Summit, NJ 07901

Dear Ms. Ng:

Please refer to your new drug application (NDA) dated and received March 25, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zeposia (ozanimod) capsules, 0.23 mg, 0.46 mg, and 0.92 mg.

This NDA provides for the use of Zeposia (ozanimod) for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

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 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>.

CARTON AND CONTAINER LABELS

Submit final printed carton and container labeling that are identical to the enclosed carton and container labels as soon as they are available, but no more than 30 days after they are printed. Please submit this labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 209899.**” Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Zeposia (ozanimod) was not referred to an FDA advisory committee because this drug is not the first in its class, the safety profile is similar to that of other drugs approved for this indication, the clinical trial designs are acceptable, the efficacy findings are clear, and the safety profile is acceptable in light of the serious nature of the disease being treated.

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.

We are waiving the pediatric studies requirement for children 0 to less than 10 years of age because necessary studies are impossible or highly impracticable. This waiver is being granted because the number of children diagnosed with relapsing forms of multiple sclerosis in that age group is small.

We are deferring submission of your pediatric studies for children 10 to less than 18 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

3809-1 A juvenile animal toxicology study of ozanimod in rat.

Draft Protocol Submission:	06/2020
Final Protocol Submission:	10/2020
Study/Trial Completion:	12/2021
Final Report Submission:	06/2022

3809-2 A two-part study of Zeposia (ozanimod) in pediatric patients with relapsing forms of multiple sclerosis (RMS) at least 10 years and less than 18 years of age. Part A is an open-label study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of Zeposia (ozanimod) in pediatric patients. Part A will include two cohorts, one with body weights less than 40 kg and the other with body weights 40 kg or more. The objective of Part A is to determine titration and maintenance doses of Zeposia (ozanimod) that will result in PK and PD effects that are comparable to those of the 8-day titration administered to adult patients. Part B is a randomized, double-blind, parallel-group study to evaluate the efficacy and safety of Zeposia (ozanimod) compared to an appropriate comparator.

Draft Protocol Submission:	03/2022
Final Protocol Submission:	08/2022
Interim/Other (Part A data):	05/2026
Study/Trial Completion:	10/2033
Final Report Submission:	03/2034

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 109159, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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>.

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 resulting 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 studies:

- 3809--3 Prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Zeposia (ozanimod) during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to Zeposia (ozanimod) before or during pregnancy and the other consisting of women without multiple sclerosis. 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.

The timetable you submitted on March 4, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2020
Final Protocol Submission:	06/2021
Annual Interim Report Submissions:	06/2022
	06/2023
	06/2024
	06/2025
	06/2026
	06/2027

	06/2028
	06/2029
	06/2030
	06/2031
Study Completion:	06/2032
Final Report Submission:	06/2033

3809--4 A pregnancy outcomes study using a different study design than provided for in PMR 3809-3 (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Zeposia (ozanimod) during pregnancy compared to an unexposed control population.

The timetable you submitted on March 4, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2020
Final Protocol Submission:	06/2021
Annual Interim Report Submissions:	06/2022
	06/2023
	06/2024
	06/2025
	06/2026
	06/2027
	06/2028
	06/2029
	06/2030
	06/2031
Study Completion:	06/2032
Final Report Submission:	06/2033

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

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess an unexpected serious risk of sudden blood pressure elevations that may lead to hypertensive crises when Zeposia

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>.

(ozanimod) is co-administered with oral tyramine. We have also determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess an unexpected serious risk of any potential effect of hepatic impairment on ozanimod's major metabolites, and to determine whether a dosing adjustment of Zeposia (ozanimod) is needed in patients with hepatic impairment.

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

- 3809-5 A randomized, double-blind, placebo-controlled, active-controlled (phenelzine), multiple-dose, parallel-group trial to investigate the pressor effect of oral tyramine during Zeposia (ozanimod) treatment in healthy subjects.

The timetable you submitted on March 17, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	05/2020
Final Protocol Submission:	11/2020
Study/Trial Completion:	02/2022
Final Report Submission:	10/2022

- 3809-6 A multiple-dose trial to assess the effect of hepatic impairment on the pharmacokinetics (PK) of Zeposia (ozanimod) and its major metabolites and to determine whether a dosing adjustment of Zeposia (ozanimod) is needed in patients with hepatic impairment. The effect of hepatic impairment on the PK of CC112273 and CC1084037 should be assessed after the 1 mg Zeposia (ozanimod) dose administration on Day 8 (following titration from 0.25 mg to 1 mg).

The timetable you submitted on March 17, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2020
Final Protocol Submission:	10/2020
Study/Trial Completion:	02/2022
Final Report Submission:	08/2022

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.⁵

Submit clinical protocols to your IND 109159 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports 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 protocols 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 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.

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for malignancies, life-threatening or fatal infections, thromboembolic vascular events, and pregnancy exposures associated with congenital renal malformations. We request that you provide expedited reports directly to your NDA (in addition to the FDA Adverse Event Reporting System) and that you include comprehensive summaries of these reports and analyses of these events as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)].

⁵ 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>.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁶

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.⁷ Information and Instructions for completing the form can be found at FDA.gov.⁸ For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁹

REPORTING REQUIREMENTS

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

⁶ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁷ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁸ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁹ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.¹⁰

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products 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.

If you have any questions, call Kristen Haslam, Regulatory Project Manager, at (240) 402-4246.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director (Acting)
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

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

¹⁰ <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>

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/

WILLIAM H Dunn
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