CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209884Orig1s000

Trade Name:	Mayzent (siponimod) tablets
Generic or Proper Name:	Siponimod
Sponsor:	Novartis Pharmaceuticals Corporation
Approval Date:	March 26, 2019
Indication:	Mayzent (siponimod) tablets 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.

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	**X**
Product Quality Review(s)	**X**
Non-Clinical Review(s)	**X**
Statistical Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209884

NDA APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Mercy Abraham, Pharm.D.
Senior Global Program Regulatory Manager
One Health Plaza, Mailstop: # 310/2150F
East Hanover, NJ 07936-1080

Dear Dr. Abraham:

Please refer to your New Drug Application (NDA) dated and received July 26, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mayzent (siponimod) tablets.

This new drug application provides for the use of Mayzent (siponimod) tablets 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 text.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. 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*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on March 22, 2019, 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 209884**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Mayzent (siponimod) 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 design was acceptable, the efficacy findings were clear, and the safety profile was 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 study requirement for ages birth up to 10 years because necessary studies are impossible or highly impracticable. This is because of the small number of patients in this age group with relapsing forms of multiple sclerosis.

We are deferring submission of your pediatric studies for ages 10 up to 17 years 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 this/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.

3591-1 Juvenile rat toxicology study to evaluate effects of siponimod on growth, reproductive development, and neurological and neurobehavioral development.

Draft Protocol Submission: 07/18
Final Protocol Submission: 04/19

Study/Trial Completion: 08/19
Final Report Submission: 02/20

3591-2 Conduct a two-part study of siponimod 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 siponimod 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 siponimod that will result in PK and PD effects that are comparable to those of the 5-day titration and the 1- or 2-mg genotype-based maintenance doses administered to adult patients. Part B is a randomized, double-blind, parallel-group study to evaluate the efficacy and safety of siponimod compared to an appropriate control.

Draft Protocol Submission: 03/20
Final Protocol Submission: 09/20
Study/Trial Completion: 09/25
Final Report Submission: 03/26

Submit the protocols to your IND 76122 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.

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 assess a known serious risk of pulmonary toxicity or identify an unexpected serious risk of teratogenicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish 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:

3591-3 A prospective, parallel cohort study in patients with relapsing forms of multiple sclerosis to assess the potentially serious risk of pulmonary toxicity. The two cohorts should consist of patients newly prescribed siponimod and patients receiving another drug used to treat relapsing forms of multiple sclerosis. The study design should minimize differences between the cohorts by defining the populations in both cohorts so that they will be similar, by ensuring that both cohorts have similar clinical assessments (specifically FEV1, FVC, and DLCO), and by ensuring that patients who discontinue treatment have continued follow-up. In addition, the study protocol should account for duration of exposure, treatment changes, and loss to follow-up. Sample size should be supported by estimates of the rates of the events of interest.

The timetable you submitted on March 19, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/20
Final Protocol Submission:	12/20
Study Completion:	12/26
Final Report Submission:	12/27

3591-4 Conduct 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 siponimod during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to siponimod 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 21, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/20
Final Protocol Submission:	09/20
Annual Interim Report Submissions:	09/21
	09/22
	09/23
	09/24
	09/25
	09/26
	09/27
	09/28
	09/29
	09/30
Study Completion:	09/31
Final Report Submission:	09/32

3591-5 Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3591-4 (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to siponimod during pregnancy compared to an unexposed control population.

The timetable you submitted on March 19, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/20
Final Protocol Submission:	09/20
Annual Interim Report Submissions:	05/21
	05/22
	05/23
	05/24
	05/25
	05/26
	05/27
	05/28
	05/29
	05/30
	05/31
Study Completion:	09/31
Final Report Submission:	09/32

Submit clinical protocols to your IND 76122 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.

We remind you of your postmarketing commitments:

3591-6 Establish an in-vitro diagnostic device to guide the use of siponimod in patients with relapsing forms of multiple sclerosis. The device should detect, at a minimum, the presence of the *2 and *3 alleles in cytochrome P450 2C9 (CYP2C9). The device should detect patients homozygous for the CYP2C9 *3/*3 genotype with statistical confidence.

The timetable you submitted on March 20, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/20
Final Protocol Submission:	12/21
Study/Trial Completion:	12/22
Final Report Submission:	12/23

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 76122 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."

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for malignancies, life-threatening or fatal infections, and thromboembolic vascular events. We request that you provide expedited reports directly to the Division of Neurology Products and that you include comprehensive summaries and analyses of these events quarterly as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)].

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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

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

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 LCDR Nahleen Lopez, Regulatory Project Manager, at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

Ellis Unger, MD
Director
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Prescribing Information
Medication Guide

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/

ELLIS F UNGER
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