DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204063

NDA APPROVAL

Biogen Idec, Inc.
Attention: Nadine D. Cohen, PhD
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your New Drug Application (NDA) dated February 24, 2012, received February 27, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tecfidera (dimethyl fumarate) delayed-release capsules, 120 mg and 240 mg.

We acknowledge receipt of your amendments dated, as follows:

February 29, 2012 (2)	June 21, 2012	August 30, 2012	November 30, 2012
April 13, 2012	June 27, 2012	September 14, 2012	December 7, 2012
April 16, 2012	June 28, 2012 (2)	October 1, 2012	December 12, 2012
April 26, 2012	July 17, 2012	October 5, 2012	January 23, 2013
May 2, 2012	July 30, 2012 (2)	October 9, 2012	January 29, 2013
May 9, 2012	July 31, 2012	October 10, 2012	February 7, 2013
May 15, 2012 (2)	August 1, 2012	October 18, 2012	February 11, 2013
May 30, 2012	August 3, 2012	October 23, 2012	February 20, 2013
June 1, 2012	August 8, 2012	October 24, 2012 (2)	February 22, 2013 (2)
June 4, 2012 (2)	August 10, 2012	October 25, 2012	February 28, 2013
June 6, 2012	August 17, 2012	October 26, 2012	March 4, 2013
June 8, 2012	August 28, 2012	November 14, 2012	March 5, 2013
June 12, 2012	August 29, 2012 (2)	November 15, 2012	March 26, 2013

This new drug application provides for the use of Tecfidera (dimethyl fumarate) delayed-release capsules, 120 mg and 240 mg, for the treatment of patients with relapsing forms of multiple sclerosis.

Expiration dating periods of 18 months for 120 mg capsules and 9 months for 240 mg capsules are assigned to this product based on the data provided in the application.

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. 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 IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the carton and immediate-container labels submitted on March 4, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204063**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Tecfidera (dimethyl fumarate) was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of patients with relapsing forms of multiple sclerosis.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement from birth to nine years of age because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients less than 10 years of age with multiple sclerosis is too small.

Additionally, we are deferring submission of your pediatric study for ages 10 through 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

2014-1 Deferred pediatric trial under PREA: A randomized, controlled, parallel group superiority trial in pediatric patients ages 10 through 17 years to evaluate the pharmacokinetics of dimethyl fumarate, and the safety and efficacy of dimethyl fumarate compared to an appropriate control for the treatment of relapsing forms of multiple sclerosis.

Final Protocol Submission:	11/30/2016
Study/Trial Completion:	10/31/2019
Final Report Submission:	02/28/2020

Submit the protocol(s) to your IND, with a cross-reference letter to this NDA. Submit the draft protocol at least 3 months prior to the final protocol submission date to allow for review and agreement on the protocol design.

Reports of this required pediatric postmarketing study must be submitted as an 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 the abuse potential of Tecfidera (dimethyl fumarate) or to identify unexpected serious risks of adverse effects on postnatal growth and development or unexpected serious risks of serious infections including opportunistic infections, leiomyomata, malignancies including renal cell cancers, and other serious adverse events including serious renal and hepatic events and other medically significant

events. 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 this serious risk.

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

2014-2 A comprehensive in vitro receptor binding study with dimethyl fumarate and with its metabolite monomethyl fumarate. This includes characterizing the affinity of dimethyl fumarate and monomethyl fumarate on dopamine, serotonin, GABA (gamma-amino-butyric-acid), opioid, NMDA, monoamine, sodium channel, calcium channel, and cannabinoid receptor sites, as well as the interaction of dimethyl fumarate and of monomethyl fumarate with nitric oxide synthase.

The timetable you submitted on March 5, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/30/2013
Study Completion:	08/30/2013
Final Report Submission:	10/30/2013

2014-3 A nonclinical self-administration study to assess abuse potential using dimethyl fumarate in animals trained to discriminate the known drug of abuse from saline. The animals chosen must demonstrate similar metabolism of dimethyl fumarate and monomethyl fumarate as observed in humans.

The timetable you submitted on March 5, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/30/2013
Study Completion:	02/28/2014
Final Report Submission:	03/30/2014

2014-4 A nonclinical discrimination study to assess abuse potential using dimethyl fumarate in animals trained to discriminate the known drug of abuse from saline. The animals chosen must demonstrate similar metabolism of dimethyl fumarate and monomethyl fumarate as observed in humans.

The timetable you submitted on March 5, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/30/2014
Study Completion:	07/30/2014
Final Report Submission:	08/30/2014

2014-5 A juvenile rat toxicology study. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study should evaluate effects of dimethyl fumarate on growth, reproductive development, and neurological and neurobehavioral development.

The timetable you submitted on March 5, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/30/2014
Study Completion:	01/31/2016
Final Report Submission:	03/31/2016

2014-6 A large, long-term, prospective observational study in adult patients with relapsing multiple sclerosis, with the primary objective of determining the nature and incidence of serious infections including opportunistic infections, leiomyomata, malignancies including renal cell cancers, and other serious adverse events including serious renal and hepatic events and other medically significant events occurring with marketed use of Tecfidera (dimethyl fumarate). The study should include characterization of the finding of urinary ketones. A minimum of 5000 multiple sclerosis patients treated with Tecfidera (dimethyl fumarate) should be enrolled and followed for a minimum of 5 years. The final protocol should reflect agency agreement and be submitted prior to starting the study.

The timetable you submitted on March 5, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/31/2013
Study Completion:	10/30/2022
Final Report Submission:	10/30/2023

Submit the protocol(s) to your IND, with a cross-reference letter to this NDA. Submit 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)"**.

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.

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 package insert to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. 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). We also request that assessment of adverse events related to abuse potential be compiled in PSURs with an emphasis on MedDRA terms and frequently used verbatim terms, as identified in Appendix B, that report incidents of euphoria-related behaviors, impaired attention, cognition, mood, and psychomotor events, and dissociative or psychotic behaviors. In addition, we request that all PSURs include specific discussions of events of potential renal toxicity, renal cell cancer, leiomyomata, and infections including opportunistic infections.

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-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action 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 Nicole L. Bradley, PharmD, Regulatory Project Manager, at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Appendix A: Content of Labeling
Appendix B: Abuse-Related Adverse Event Terms

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
03/27/2013