DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125104/S-958

SUPPLEMENT APPROVAL

Biogen, Inc.
Attention: Trevor Mill
Senior Vice President, Regulatory Affairs
225 Binney Street
Cambridge, MA 02142

Dear Mr. Mill:

Please refer to your Supplemental Biologics License Application (sBLA), dated July 19, 2016, received July 19, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for Tysabri (natalizumab).

This prior approval supplemental biologics application provides for proposed modifications to the approved risk evaluation and mitigation strategy (REMS). This supplement is in response to our May 18, 2016, REMS Modification Notification letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Tysabri (natalizumab) was originally approved on October 7, 2011, and the most recent modification was approved on May 12, 2015. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In order to ensure the benefits of Tysabri (natalizumab) outweigh its risks, we determined that you were required to make the following REMS modifications:

- Changes to the REMS to be consistent with safety labeling changes approved on May 18, 2016. The approved safety labeling changes included the addition of the following within Section 5.1—Progressive Multifocal Leukoencephalopathy:

> "*Periodic monitoring for radiographic signs consistent with PML should be considered to allow for an early diagnosis of PML. Lower PML-related mortality and morbidity have been reported following Tysabri discontinuation in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis.*"

Your proposed modifications to the REMS consisted of changes to the REMS document, REMS enrollment forms, and educational materials to incorporate this new information. You also proposed additional changes, as follows:

- Changes throughout the REMS document and all REMS materials to reflect the sponsor name change from Biogen Idec to Biogen.
- Changes throughout the materials to update the list of immunosuppressants, antineoplastics, and immunomodulators with a recently approved medication for multiple sclerosis (Zinbryta [daclizumab]).
- Changes to the signature statements found on the reauthorization and discontinuation status forms to enable certified prescribers to delegate the completion of the forms to individuals within their office who are not certified prescribers.
- Format and editorial changes, typographical corrections, and updated version and copyright dating throughout the REMS materials.
- Deletion of the REMS call center hours of availability from all REMS materials.

Your proposed modified REMS, submitted on September 20, 2016, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on October 7, 2011.

There are no changes to the REMS assessment plan described in our March, 3, 2015, letter.

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 the 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:

BLA 125104 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

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:

BLA 125104 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125104/SECONDARY TRACKING NUMBER
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125104/SECONDARY TRACKING NUMBER
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125104/SECONDARY TRACKING NUMBER
PRIOR APPROVAL SUPPLEMENT

PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125104/SECONDARY TRACKING NUMBER
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 BLA 125104

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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Nahleen Lopez, Regulatory Project Manager, at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

Alice Hughes, MD
Deputy Director for Safety
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
REMS

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

/s/

ALICE HUGHES
09/22/2016