DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125104/S-960/S-963

SUPPLEMENT APPROVAL

Biogen
Attention: Trevor Mill
Senior Vice President, Global Regulatory Sciences
225 Binney Street
Cambridge, MA 02142

Dear Mr. Mill:

Please refer to your Supplemental Biologics License Applications (sBLAs), dated and received October 16, 2017, and December 21, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for Tysabri (natalizumab).

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated October 5, 2017.

These Prior Approval supplemental biologics applications provide for the following revisions:

- Revisions to Section 5.1 (Warnings and Precautions; Progressive Multifocal Leukoencephalopathy [PML]) to update the language pertaining to MRI monitoring and to indicate that, based on retrospective analyses of postmarketing data from various sources, the risk of developing PML may be associated with relative levels of serum anti-JC Virus (JCV) antibody compared to a calibrator as measured by ELISA (often described as an anti-JCV antibody index value)
- Revisions to Section 5.6 (Warnings and Precautions; Immunosuppression/Infections) to incorporate information about opportunistic infections observed in a long-term safety study of patients treated with Tysabri for multiple sclerosis
- Revisions throughout the prescribing information and carton and vial label to change “Single Use” to “Single-Dose” in accordance with the “Guidance for Industry: Selection of Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use”
- Revisions to Section 16 (How Supplied/Storage and Handling) to incorporate a summary statement pertaining to Tysabri storage
- Proposed modifications to the approved Tysabri risk evaluation and mitigation strategy (REMS)

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are 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, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the prescribing information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on March 28, 2018, 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3).* For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125104/S-963**." Approval of this submission by FDA is not required before the labeling is used.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Tysabri (natalizumab) was originally approved on October 7, 2011, and the most recent REMS modification was approved on September 22, 2016. 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.

Your proposed modifications to the REMS consist of:

- Changes to selected REMS materials to reflect the revisions to the prescribing information being approved, specifically the addition of information noting that the risk of developing PML may be associated with relative levels of serum anti-JCV antibody compared to a calibrator as measured by ELISA (often described as an anti-JCV antibody index value). This information has been included in the *TOUCH Prescribing Program Educational Slide Deck*, and the following statement has been added to selected REMS forms (the *Prescriber/Patient Enrollment Forms*, the *Patient Status Report and Reauthorization Questionnaires*, the *Initial Discontinuation Questionnaires*, and the *6-Month Discontinuation Questionnaire [MS]*): "If an anti-JCV antibody index value is available, please record it here:__".
- Removal of 12-Week Questionnaire for Crohn's Disease from the REMS.
- Changes to REMS educational materials to align with labeling changes approved on August 16, 2017, pertaining to JCV granule cell neuronopathy, MRI monitoring for PML, anti-JCV antibody testing following use of intravenous immunoglobulin, and acute retinal necrosis caused by herpes viruses.
- Minor formatting changes and editorial revisions.

Your proposed modified REMS, submitted on April 18, 2018, amended 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.

The revised REMS assessment plan must include, but is not limited to, the following:

The annual Tysabri REMS assessment report must contain the following information:

For the current and previous REMS reporting periods, provide the following information. Where applicable, a tabular format is acceptable.

I. TYSABRI REMS Program enrollment and certification
   a. Newly enrolled and active patients
   b. Newly enrolled and active Crohn's disease patients
   c. Newly certified and active certified prescribers
   d. Newly certified and active certified pharmacies
   e. Newly certified and active certified infusion centers

II. Documentation of safe use conditions
   a. Duration of Tysabri use by patients who were active during the current reporting period, by two year intervals: 0-24 months, >24 months, etc.

b. Concurrent use of antineoplastics, immunomodulatory, or other immunosuppressive agents: Number and proportion of active patients who are taking one or more of these medications during the current and previous REMS reporting periods

III. REMS Program Compliance (infrastructure and performance)
   a. Number of patients not enrolled into the TYSABRI REMS but who were administered TYSABRI
   b. Pre-infusion patient checklists
      i. Number of Pre-infusion Patient Checklists with a "yes" response to the questions 1 through 3 for MS and CD
      ii. Number of infusions administered without physician authorization
      iii. Number of infusions administered when physician could not be contacted
      iv. Reauthorization: number of patients administered TYSABRI outside of the reauthorization period
      v. Number of patients whose infusion was not administered on-time due to a "yes" response to questions 1-3, reason for delay, and duration (mean and range) of delays
   c. Discontinuations
      i. Number of initial discontinuation forms submitted during the reporting period
      ii. Number of follow-up discontinuation forms submitted during the reporting period
      iii. Number of outstanding discontinuation forms during the reporting period
      iv. New cases of PML or death identified as result of submission of discontinuation forms
      v. Number and proportion of patients who discontinued during the reporting period for whom recommended follow-up was not achieved (lost-to-follow-up)
   d. Number of prescribers, infusion centers, or pharmacies removed from the REMS program during the current reporting period; reasons for removal and a brief description of the actions taken
   e. Audits conducted during the reporting period: Summarize audits conducted, findings, and actions taken to address non-compliance found during audits

IV. PML: Include the most current table (i.e., an updated version of the table that currently appears in labeling as Table 1), showing the estimated incidence of PML stratified by the three known risk factors (duration of Tysabri exposure, anti-JCV antibody status, and history of prior immunosuppressant use).

V. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

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 that 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 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

or

NEW SUPPLEMENT FOR BLA 125104/ S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125104/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125104/ S-000
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/ S-000
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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email REMS_Website@fda.hhs.gov.

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 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 601.12(f)(4), 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 BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call LCDR 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):
Content of Labeling
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
04/18/2018