



BLA 125104/S-950

SUPPLEMENT APPROVAL

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

Dear Dr. Cohen:

Please refer to your Supplemental Biologics License Application (sBLA), dated November 11, 2014, received November 12, 2014, submitted under section 351(a) of the Public Health Service Act for Tysabri (natalizumab).

We acknowledge receipt of your amendments dated November 24, 2014, December 12, 2014, January 23, 2015, April 24, 2015, April 28, 2015, May 5, 2015, and May 8, 2015. We also acknowledge your risk evaluation and mitigation strategy (REMS) assessment dated October 7, 2014.

This supplemental application provides for revisions to the Tysabri Prescribing Information and Medication Guide and proposed modifications to the approved REMS. The labeling revisions include a revision to Table 1 in Section 5.1, Progressive Multifocal Leukoencephalopathy (PML). The estimated incidence of PML in the United States stratified by risk factor has been updated based on more recent postmarketing data.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

In addition, we have found the REMS assessment to be adequate.

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 package insert 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Tysabri was originally approved on October 7, 2011, and the most recent modification was approved on December 15, 2013. 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 the Medication Guide and REMS forms and materials to be consistent with revisions to approved labeling. In addition, the following modifications were made:

- All appended REMS materials were updated to reflect your current trademark guidelines and the new version number.
- The Prescriber-Patient Enrollment Forms and Pre-Infusion Patient Checklists were updated to include products approved for multiple sclerosis and Crohn’s disease since the last REMS modification.
- The Patient Status Report and Reauthorization Questionnaires and the Patient Initial Discontinuation Questionnaire—CD were updated to include new products in the lists of immunomodulatory or immunosuppressant products the patient currently receives or has received in the previous 6 months.

Your proposed modified REMS, submitted on May 8, 2015, and appended to this letter, is approved.

The modified REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS will remain 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). 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 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)**

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

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**

< other supplement identification >

PROPOSED MINOR REMS MODIFICATION

Or

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

< other supplement identification >

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**

< other supplement identification >

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 Hamet Touré, PharmD MPH, Regulatory Project Manager, at (301) 796-7534.

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

ENCLOSURES:

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
05/12/2015