DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125104/S-953
BLA 125104/S-955

SUPPLEMENT APPROVAL
REMS MODIFICATION NOTIFICATION

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 November 17, 2015, received November 18, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for Tysabri (natalizumab).

This Prior Approval supplemental biologics license application (S-953) provides for the following revisions to the labeling:

- The addition of the following in Section 5.5 (Hypersensitivity/Antibody Formation): "Patients who receive TYSABRI for a short exposure (1 to 2 infusions) followed by an extended period without treatment are at higher risk of developing anti-natalizumab antibodies and/or hypersensitivity reactions on re-exposure, compared to patients who received regularly scheduled treatment."

- The addition of the mean decrease in hemoglobin observed in the MS placebo-controlled pivotal trials of natalizumab in Section 5.7 (Laboratory Test Abnormalities)

We also refer to our letter dated March 8, 2016, notifying you, under Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA), of new safety information that we believe should be included in the labeling for Tysabri (natalizumab). This information pertains to the risk of progressive multifocal leukoencephalopathy (PML). New data indicate that patients who are asymptomatic at PML diagnosis may have better outcomes than those with characteristic PML signs and symptoms at diagnosis, including a decreased rate of PML-related mortality.[1] These data indicate that periodic MRI monitoring may be valuable.

[1] Dong-Si T, Richman S, Wattjes MP, et al. Outcome and survival of asymptomatic PML in natalizumab-treated MS patients. Ann Clin Transl Neurol. 2014 Oct;1(10):755-64.

We refer to your sBLA (S-955), dated and received April 7, 2016, submitted under section 351(a) of the Public Health Service Act. This sBLA, submitted following our March 8, 2016, letter notifying you of the new safety information regarding PML that we believe should be included in the labeling for Tysabri (natalizumab), provides for revisions to the labeling for Tysabri. The agreed-upon changes to the original language included in our March 8, 2016, letter are as follows (additions to the language being included within Section 5.1—Progressive Multifocal Leukoencephalopathy are noted by underline and deletions are noted by ~~strikethrough~~):

> "MRI findings may be apparent before clinical signs or symptoms. Cases of (b) (4) PML, diagnosed based on MRI findings and the detection of JCV DNA in the CSF in the absence of clinical signs or symptoms specific to PML, have been reported. Many of these patients subsequently became symptomatic. 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. It is not known whether these differences are due to early detection and discontinuation of Tysabri or due to differences in disease in these patients."

The final labeling differs from the March 8, 2016, letter by the deletion of (b) (4) prior to "PML" in the description of the cases of PML that were diagnosed based on MRI findings and the detection of JCV DNA in the CSF in the absence of clinical signs or symptoms specific to PML.

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 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.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENT

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

We also refer to our letter dated March 8, 2016, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Tysabri (natalizumab), and the approval of the safety labeling changes with this action. Those labeling changes pertain to the risk of progressive multifocal leukoencephalopathy (PML).

In accordance with section 505-1(g)(4)(B) of the FDCA, we have determined that your approved REMS for Tysabri (natalizumab) must be modified to ensure that the benefits of the drug outweigh its risks. This determination is based on the need to conform the approved REMS to the safety labeling changes approved with this action.

Your proposed modified REMS must include changes to the REMS, including changes to REMS forms and materials, to be consistent with revisions to approved labeling, which, as described above, include 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."

The timetable for submission of assessments of the proposed modified REMS may remain the same as that approved on October 7, 2011.

The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised.

In addition, the submission should include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a modified REMS as described above is necessary to ensure the benefits of Tysabri (natalizumab) outweigh the risks, you must submit a proposed REMS modification within 60 days of the date of this letter.

Submit the proposed modified REMS as a Prior Approval supplement (PAS) to your BLA.

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B), you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR BLA ######/SECONDARY TRACKING NUMBER
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT 955

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

BLA ######/SECONDARY TRACKING NUMBER
PROPOSED REMS MODIFICATION-AMENDMENT

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 your submission.

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(s) 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 package insert(s), 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.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above, by fax to 301-847-8444, or 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).

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, M.D.
Deputy Director for Safety
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling

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
05/18/2016