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**SUPPLEMENT APPROVAL
REMS ASSESSMENT ACKNOWLEDGMENT**

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 Supplemental Biologics License Applications (sBLA) for Tysabri (natalizumab) dated November 14, 2012 and received November 15, 2012, dated December 11, 2012 and received December 12, 2012, and dated June 21, 2012, and received June 21, 2012, which were submitted under section 351(a) of the Public Health Service Act.

We acknowledge receipt of your amendments dated January 7, 2013, May 30, 2013, July 9, 2013, July 15, 2013, October 8, 2013, October 17, 2013, November 1, 2013, November 21, 2013, December 3, 2013, December 12, 2013, and December 13, 2013. We also acknowledge your risk evaluation and mitigation strategy (REMS) assessment dated October 17, 2013.

These supplemental applications propose the following changes:

- | | |
|-----|---|
| 840 | Prior Approval supplemental biologics application to provide information regarding the use of Tysabri in the anti-JCV antibody negative population and corresponding proposed modifications to the approved risk evaluation and mitigation strategy (REMS). |
| 847 | Changes Being Effected supplement to revise section 5.1, Progressive Multifocal Leukoencephalopathy (PML), in which the PML risk stratification algorithm for patients who are anti-JCV antibody positive has been updated in Table 1. |
| 889 | Prior Approval labeling supplement to revise Section 5.1, Progressive Multifocal Leukoencephalopathy (PML), in which the PML risk |

stratification algorithm for patients who are anti-JCV antibody positive has been updated in Table 1 to include an additional row that shows the PML risk estimate for anti-JCV antibody positive patients without prior immunosuppressant (IS) use who have received 49 to 72 infusions of TYSABRI.

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.

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

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Tysabri (natalizumab) was originally approved on October 7, 2011, and REMS modifications were approved on January 20, 2012 and May 24, 2013. The REMS consists of a Medication Guide, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of revisions to the REMS document, multiple REMS forms and materials, and the Medication Guide to reflect the revision to the indication statement language and the new risk information regarding hepatotoxicity, meningitis, and encephalitis being approved with these supplements.

Your proposed modified REMS, submitted on December 13, 2013, and appended to this letter, is approved.

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 August 17, 2012, letter.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

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

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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 the 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
PROPOSED REMS MODIFICATION**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125104
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

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

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:

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 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. 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>.

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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 or by fax to 301-847-8444.

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

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Acting Division Director
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/

ERIC P BASTINGS
12/15/2013