DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125104-813

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 Application (sBLA), dated and received August 9, 2012, submitted under section 351(a) of the Public Health Service Act for Tysabri (Natalizumab) injection.

We also refer to your amendments dated April 2, 2013, and April 23, 2013.

We acknowledge your risk evaluation and mitigation strategy (REMS) assessment dated October 5, 2012.

Supplement 813 is a "Prior Approval" supplemental biologics application proposing labeling and REMS changes related to monitoring of PML after discontinuation of Tysabri (natalizumab).

We have completed our review of these supplemental applications. 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. Content of labeling must be 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 a REMS modification was approved on January 20, 2012. The REMS consists of a Medication Guide, communication plan, 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 changes to the Medication Guide and REMS document to include information about monitoring of PML after discontinuation of Tysabri (natalizumab), and corresponding updates to the REMS materials (e.g., Prescriber/Patient Enrollment Forms and Reauthorization and Discontinuation Questionnaires for Multiple Sclerosis and Crohn's Disease patients and the Understanding PML for Gastroenterologists document). You have also proposed modifications to your REMS assessment plan, which will be addressed separately.

Your proposed modified REMS, submitted on August 9, 2012, 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.

The REMS assessment plan will remain the same as that delineated in our General Advice Letter dated August 17, 2012:

1. For all of the reporting categories within the RiskMAP reports, provide totals for the current REMS assessment reporting period and as a cumulative total from start of the RiskMAP program.

a. For new data categories in the REMS assessment plan, the cumulative data should be provided from start of the REMS program (beginning with the second report).
b. Beginning with the second report, provide three tallies: current reporting period, cumulative from start of the RiskMAP, and cumulative since start of the REMS.

2. An assessment of use data for Tysabri (during the reporting period and cumulative), including at a minimum:
    a. The extent of use in the indicated populations
    b. The extent of use in patients by various baseline data parameters (e.g., baseline demographics) in the TOUCH Prescribing Program (i.e., summary statistics on age, gender, relapsing multiple sclerosis (MS) diagnosis, or moderately to severely active Crohn's Disease (CD) diagnosis, most recent MS or CD therapy, any prior Tysabri exposure)

3. An assessment of enrollment into the TOUCH Prescribing Program (during the reporting period and cumulative):
    a. Number of patients enrolled
    b. Number of patient person-years for enrolled patients
    c. Number of new patients enrolled
    d. Number of patients who were not enrolled and received Tysabri
    e. Number of patients who were lost to follow-up
    f. Number of healthcare providers enrolled
        i. Number of new healthcare providers enrolled
        ii. Number of healthcare providers who prescribed Tysabri and were not enrolled
    g. Number and types of pharmacies enrolled
    h. Number of infusion sites enrolled

4. Tysabri infusion data (during the reporting period and cumulative):
    a. Number and percent of Pre-infusion Patient Checklists received by Biogen
        i. Number of Pre-infusion Patient Checklists with a "yes" response to the questions 1 through 3 for MS and CD patients
        ii. Number of patients who were infused despite a "yes" response to items 1 through 3 on the Pre-infusion Patient Checklist
        iii. Number of patients for whom infusion was withheld for any reason other than doctor's orders
        iv. Number of patients for whom prescriber was contacted
        v. Number of patients for whom prescriber was unable to be contacted
        vi. Method for determining the number of expected forms
        vii. Total number of Tysabri infusions
    b. Proportion of patients who are receiving concurrent antineoplastics, immunomodulatory, or immunosuppressant agents (including systemic corticosteroids), and time of exposure to such therapies

5. Patient Status Report and Reauthorization Questionnaire Data

a. Percent and Number of Tysabri Patient Status and Re-Authorization Questionnaires completed compared to the number of questionnaires sent
b. Number of Tysabri patients dosed outside of the re-authorization period
c. Proportion of patients who received more than 6 consecutive months of systemic corticosteroids within the past year (CD only)
d. Proportion of patients that were unable to fully taper off their systemic corticosteroids within 6 months after starting Tysabri and the proportion of that subset of patients in whom Tysabri was discontinued (CD only)
e. Proportion of patients who required (other than the initial 6-month taper) additional corticosteroid use that exceeded 3 months in a calendar year, and the proportion of that subset of patients in whom Tysabri was discontinued (CD only)

6. Tysabri discontinuation data
    a. Number of patients who discontinued Tysabri
    b. Number and percent of discontinuation forms received and the number expected
    c. How the expected number of discontinuation forms received is calculated
    d. Percent and number of 12-Week Questionnaires completed compared to questionnaires sent (CD)
    e. Percent and number of patients who did/did not experience a therapeutic benefit within 12 weeks of starting Tysabri (CD)
    f. Percent and number of patients in which the prescriber did/did not continue Tysabri treatment (CD)
    g. Proportion of patients that were unable to fully taper off of their systemic corticosteroids within 6 months after starting Tysabri, and the proportion of that subset of patients in whom Tysabri was discontinued (CD)
    h. Proportion of patients that required (other than the initial 6-month taper) additional steroid use that exceeded 3 months in a calendar year, and the proportion of that subset of patients in whom Tysabri was discontinued (CD)
    i. Number of patients re-enrolled

7. Safety assessments
    a. An assessment of all PML cases (suspected and diagnosed)
        i. The listings and aggregate summary data for all suspected and diagnosed PML cases including all PML-related deaths
        ii. PML incidence data
    b. An analysis of other serious opportunistic infections
    c. An analysis of the data collected from the reauthorization forms pertaining to malignancy
    d. Where clinical data are incomplete concerning events of interest (e.g., PML suspected or diagnosed), other serious opportunistic infections [OI] or other data points of interest, the report will include a complete description of Biogen's attempts to obtain the missing data.

8. Knowledge and Behavior Survey data
    a. Prescribers' understanding of safe use of Tysabri including approved indications,contraindications, and risk of PML

b. Patients' understanding of the risk of PML associated with Tysabri
c. Infusion nurse knowledge and behavior regarding Tysabri use, such as patient selection and checking the Pre-infusion Patient Checklist prior to each infusion

9. Compliance Assessments
    a. The number of enrolled prescribers, infusion sites, and pharmacies for the reporting period and cumulatively
    b. The number and type of deviations (short of de-enrollment), with description and corrective actions for each case, for prescribers, infusion sites, or pharmacies
    c. The number of prescribers, infusion sites, or pharmacies de-enrolled and reenrolled,the reasons for each de-enrollment, and the basis for each re-enrollment for the reporting period and cumulatively
    d. A summary report of pharmacy, infusion site, and distributor audits conducted during the reporting period, stratified by facility type
        i. The number of audits of each stakeholder type (prescribers, infusion sites, pharmacy providers, pharmacies by type, distributor)
        ii. An analysis of data commonly missing or inaccurate on inventory tracking logs, including how Biogen reconciles missing data
        iii. An analysis of infusion site compliance with submission of the completed Pre-Infusion Patient Checklist
        iv. An analysis of any other deviations found and corrective actions taken
    e. An assessment of prescriber compliance with elements of certification: completing enrollment forms, reauthorization forms, and complying with discontinuation procedures

10. General
    a. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified
    b. A report on periodic assessments of the dispensing of the Medication Guide in accordance with 21 CFR 208.24

In addition to the assessments submitted according to the timetable included in the approved REMS, 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.

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 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.

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

Sincerely,

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center of 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
05/24/2013