DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

STN: BL 125104/570

SUPPLEMENT APPROVAL

Biogen Idec, Inc.
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 (BLA) dated September 19, 2008, received September 22, 2008, submitted under section 351 of the Public Health Service Act for Tysabri (natalizumab). We note that BLA 125104 was approved under the provisions of 21 CFR 601.42 (Subpart E).

This supplemental application provides for a proposed risk evaluation and mitigation strategy (REMS) for Tysabri (natalizumab) and was submitted in accordance with section 909(b)(1) of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under section 909(b)(1) of FDAAA, we identified Tysabri (natalizumab) as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 601 (Subpart E).

We also refer to our correspondences dated October 10, 2009, October 29, 2010, June 4, 2011, June 7, 2011, July 25, 2011 (2), September 1, 2011, September 20, 2011, September 22, 2011, September 23, 2011 (3), September 27, 2011 (2), and to your correspondence and submissions dated October 23, 2009, December 13, 2010, July 15, 2011, August 10, 2011, September 8, 2011, September 27, 2011, and September 28, 2011.

In accordance with section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that a REMS is necessary for Tysabri (natalizumab) to ensure that the benefits of the drug outweigh the risk of progressive multifocal leukoencephalopathy (PML).

Your proposed REMS, as amended and appended to this letter, is approved. 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.

The REMS Assessment Plan should include, but is not limited to, the following information:

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; for these patients, include information pertaining to duration of treatment delay, and any changes in clinical status of the patient
        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. Reason for discontinuation (e.g., death, adverse event, loss to follow-up, lack of efficacy)
c. Number and percent of discontinuation forms received and the number expected
d. How the expected number of discontinuation forms received is calculated
e. Percent and number of 12-Week Questionnaires completed compared to questionnaires sent (CD)
f. Percent and number of patients who did/did not experience a therapeutic benefit within 12 weeks of starting Tysabri (CD)
g. Percent and number of patients in which the prescriber did/did not continue Tysabri treatment (CD)
h. 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)
i. 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)
j. Number of patients experiencing worsening of disease due to treatment interruptions
k. Number of patients re-enrolled

7. Safety assessments

a. An assessment of all PML cases (suspected and diagnosed)
    i. The listings and case narratives for all suspected 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 re-enrolled, the reasons for each de-enrollment, and the basis for each re-enrollment for the reporting period and cumulatively
    - The number of unintended therapy interruptions resulting from de-enrollment. The report should include follow-up data on disposition, duration, and outcome including any related or possibly related adverse outcomes. Indicate those reported to MedWatch as serious unlabeled Adverse Events.
d. A summary and analysis of unintended interruptions in treatment (e.g., interruptions due to shipment delays) and any corrective actions taken
e. A summary report of pharmacy, infusion site, and distributor audits conducted during the reporting period, stratified by facility type
    - The number of audits of each stakeholder type (prescribers, infusion sites, pharmacy providers, pharmacies by type, distributor)
    - An analysis of data commonly missing or inaccurate on inventory tracking logs, including how Biogen reconciles missing data
    - An analysis of infusion site compliance with submission of the completed Pre-Infusion Patient Checklist
    - An analysis of any other deviations found and corrective actions taken

f. 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
c. Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that 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 FDCA.

Prominently identify the amendment containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125104 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125104
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

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.

As part of the approval under Subpart E, as required under 21 CFR 601.45, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days before the intended time of initial distribution of the labeling or initial publication of the advertisement. Send one copy to the Division of Neurology Products and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please refer to http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact LCDR Hamet Touré, PharmD MPH, Regulatory Project Manager, at (301) 796-7534.

Sincerely,

/ Russell Katz /
Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center of Drug Evaluation and Research

Attachments:
Content of labeling
REMS
REMS Materials