BLA 125104/S-977

SUPPLEMENT APPROVAL

Biogen, Inc.
Attention: Priya Singhal
Senior Vice President, Global Safety and Regulatory Sciences
225 Binney Street
Cambridge, MA 02142

Dear Ms. Singhal:

Please refer to your supplemental biologics license application (sBLA), dated and received November 14, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Tysabri (natalizumab).

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Tysabri (natalizumab) was originally approved on October 7, 2011, and the most recent REMS modification was approved on April 11, 2023. 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 pertains to the risk of progressive multifocal leukoencephalopathy (PML).

In order to ensure the benefits of Tysabri outweigh its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification letter dated September 15, 2022. The required modification resulted in changes to the following materials:

- REMS Document
- Prescriber Enrollment Form
- Patient Enrollment Form – Multiple Sclerosis
- Patient Enrollment Form – Crohn's Disease
- Pharmacy Enrollment Form
- Infusion Site Enrollment Form
- Educational Slide Set
- Overview
- Understanding PML for Gastroenterologists – Crohn's Disease
- Pre-Infusion Patient Checklist

- Patient Status Report and Reauthorization Questionnaire
- Initial Discontinuation Questionnaire
- 6-Month Discontinuation Questionnaire

Your proposed modified REMS, submitted on November 14, 2022, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on October 7, 2011.

The revised REMS assessment plan must include, but is not limited to, the following:

Program Implementation and Operations

I. Tysabri REMS Program enrollment and certification (provide 2 previous, current, and cumulative reporting periods)
   a. Newly enrolled and active Multiple Sclerosis (MS) patients
   b. Newly enrolled and active Crohn's disease (CD) patients
   c. Total number of unique patients newly enrolled
   d. Total number of unique active patients
   e. Newly certified and active certified prescribers
   f. Newly certified and active certified pharmacies
   g. Newly certified and active certified infusion sites

II. Shared Database Platform
   a. Newly enrolled and active patients
   b. Documentation of prior natalizumab exposure
      i. Newly enrolled patients with MS confirmed as a match
      ii. Newly enrolled patients with CD confirmed as a match
      iii. Number of matched patients with MS and prior natalizumab history with a diagnosis of PML
      iv. Number of matched patients with CD and prior natalizumab history with a diagnosis of PML
   c. Number of unique patients of all active patients that switched natalizumab products including:
      i. The number of times the unique patients switched between products (stratified by number of unique patients switch)

III. Infrastructure and Performance (to be reported for the first two years post-launch of the shared database)
   a. REMS Program Call Center
      i. Summary report of REMS-related problems related to the shared database identified

ii. Stakeholder type for calls that may indicate an issue with access or burden related to the shared database (e.g., any identified burden or access issues associated with the shared database)
    a) Provide outcome of the call, including any actions taken for the identified issue as appropriate

IV. REMS Program Compliance (infrastructure and performance) (provide 2 previous, current, and cumulative reporting periods)

a. Number of patients not enrolled into the Tysabri REMS but who were administered Tysabri [stratify by on-site (health care settings) and in-home administrations]
b. Pre-infusion patient checklists [stratify by on-site (health care settings) and in-home administrations]:
    i. Number of Pre-infusion Patient Checklists with a “yes” response to the questions 1 through 3 for MS and CD
    ii. Number of infusions administered without physician authorization
    iii. Number of infusions administered when physician could not be contacted
    iv. Reauthorization: number of patients administered Tysabri outside of the reauthorization period
    v. Number of patients whose infusion was not administered on-time due to a “yes” response to questions 1-3, reason for delay, and duration (mean and range) of delays
c. Discontinuations
    i. Number of initial discontinuation forms submitted during the reporting period
    ii. Number of follow-up discontinuation forms expected during the reporting period
    iii. Number of follow-up discontinuation forms submitted during the reporting period
    iv. Number of outstanding discontinuation forms during the reporting period
    v. Number and proportion of patients who discontinued during the reporting period for whom recommended follow-up was not achieved (lost-to-follow-up)
d. Number of prescribers, infusion sites, or pharmacies removed from the REMS program during the current reporting period; reasons for removal and a brief description of the actions taken
e. Listing of total number of non-compliance identified for prescribers, pharmacies, and infusion sites
    i. Total non-compliance based on each stakeholder type listed above
    ii. Category (Critical Event, Major Event, Minor Event)

iii. Number of occurrences based on category
iv. The action(s) taken in response to noncompliance

f. Audits conducted during the reporting period: Summarize audits conducted, findings, and actions taken to address non-compliance found during audits
    i. Summary of audit activities including:
        a) The number of risk-based audits planned, and the number of risk-based audits completed for each stakeholder type
        b) The number and types (Classification [Critical, Major, Minor]) of deficiencies noted by stakeholder type for completed audits
        c) Listing of Corrective Actions and Preventative Actions (CAPAs) for any stakeholder non-compliance identified during the audits, including the Overall Target CAPA Due Date or CAPA Closure Date, and the individual Action Completion Dates

g. Shared Database
    i. The number of times real-time data sharing regarding natalizumab-PML risk factors between REMS programs for patient data exceeded 72 hours from the initial query
    ii. The number of times the shared system database was unavailable, including the dates, length of time for which the database was unavailable
        a) Include a root cause analysis to determine why the shared database was unavailable
        b) Include corrective actions implemented to prevent future occurrences
    iii. Report on Back-up Open Communication Process
        a) Number of times the process was implemented
        b) Number of unique patients for whom the process had to be implemented
        c) Analysis if the process was effective in identifying and matching switch patients

Safe Use Behaviors

V. Documentation of safe use conditions (provide 2 previous, current, and cumulative reporting periods)
    a. Duration of Tysabri use by patients who were active during the current reporting period, by two year intervals: 0-24 months, >24 months, etc.
    b. Concurrent use of antineoplastics, immunomodulatory, or other immunosuppressive agents: Number and proportion of active patients

who are taking one or more of these medications during the current and previous REMS reporting periods

c. For matched patients from the data exchange platform, duration of natalizumab (Tysabri and other approved natalizumab products) by patients who were active during the current reporting period, by two-year intervals: 0-24 months, >24 months, etc.
d. For in-home infusions, provide the number of unique patients and the number of infusions received (1-12, >12)

Health Outcomes and/or Surrogates of Health Outcomes

VI. Progressive Multifocal Leukoencephalopathy (PML):
   a. Include the most current table (i.e., an updated version of the table that currently appears in labeling as Table 1), showing the estimated incidence of PML stratified by the three known risk factors (duration of natalizumab [Tysabri and other approved natalizumab products] exposure, anti-JCV antibody status, and history of prior immunosuppressant use)
   b. New cases of PML or death identified as result of submission of discontinuation forms
   c. New cases of PML or death reported in the Periodic Safety Update Report (PSUR)
   d. New cases of PML identified in a confirmed switch patient stratified by cumulative duration of natalizumab, anti-JCV antibody status, and history of prior immunosuppressant use

Knowledge

VII. Knowledge, Attitude and Behavior survey data (provide every two years starting with the 2019 assessment report)
   a. Prescribers' understanding of the 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 site healthcare provider knowledge and behavior regarding Tysabri use, such as patient selection and checking the Pre-infusion Patient Checklist prior to each infusion.

Overall Assessment of REMS Effectiveness

VIII. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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) of the FDCA. 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 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 ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

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

or

NEW SUPPLEMENT FOR BLA 125104/ S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125104/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125104/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125104/ S-000
REMS ASSESSMENT
PROPOSED 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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

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 Kristen Haslam, Regulatory Project Manager, at 240-402-4246.

Sincerely,

{See appended electronic signature page}

Paul R. Lee, MD, PhD
Director
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- REMS

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PAUL R LEE
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