BLA 125104/S-976 and S-979

SUPPLEMENT APPROVAL

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

Dear Dr. Singhal:

Please refer to your supplemental biologics license application (sBLA), dated and received July 27, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Tysabri (natalizumab) injection, for intravenous use.

This Prior Approval supplemental biologics application provides for revisions to Section 5.2 (Warnings and Precautions; TYSABRI TOUCH Prescribing Program) of the Tysabri Prescribing Information (PI), revisions to the Medication Guide to allow for in-home infusion, and proposed modifications to the approved Tysabri risk evaluation and mitigation strategy (REMS), including clarifications for the database requirements.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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 Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 (which includes new salts and new fixed combinations), 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 (REMS) REQUIREMENTS

The REMS for Tysabri was originally approved on October 7, 2011, and the most recent REMS modification was approved on December 10, 2021. 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.

Your proposed modifications included changes to the REMS document and materials to align with the labeling changes being approved to allow for in-home infusions and additional changes to separate the joint Prescriber/Patient Enrollment Forms (MS) (CD) into a Prescriber Enrollment Form, Patient Enrollment Form (MS) and Patient Enrollment Form (CD), as well as to streamline the materials. In addition, the scope of the database requirement has been clarified.

The following documents are being revised:

- REMS Document
- Pre-Infusion Patient Checklist
- Pharmacy Enrollment Form

- Infusion Site Enrollment Form
- TOUCH Prescribing Program Overview
- TOUCH Prescribing Program Educational Slide Set
- Prescriber/Patient Enrollment Form (MS)
- Helpful Information for Evaluation of New Neurological Symptoms in Patients Receiving Tysabri
- Patient Status Report and Reauthorization Questionnaire (MS)
- Initial Discontinuation Questionnaire (MS)
- 6-Month Discontinuation Questionnaire (MS)
- Change Prescriber Authorization Form
- Prescriber Patient Enrollment Form (CD)
- Understanding PML for Gastroenterologists
- Patient Status Report and Reauthorization Questionnaire (CD)
- Initial Discontinuation Questionnaire (CD)
- 6-Month Discontinuation Questionnaire (CD)
- REMS Program Website Screenshots

Your proposed modified REMS, submitted on July 27, 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 patients
   b. Newly enrolled and active Crohn's disease patients
   c. Newly certified and active certified prescribers
   d. Newly certified and active certified pharmacies
   e. Newly certified and active certified infusion sites

II. 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 submitted during the reporting period
   iii. Number of outstanding discontinuation forms during the reporting period
   iv. 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. Audits conducted during the reporting period: Summarize audits conducted, findings, and actions taken to address non-compliance found during audits

Safe Use Behaviors

III. 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 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

IV. 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 Tysabri 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)

Knowledge

V. 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

VI. 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 REMS 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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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-related information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4).

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

Sincerely,

{See appended electronic signature page}

[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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Alice T.D. Hughes, MD
Deputy Director for Safety
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Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- REMS

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/

ALICE HUGHES
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