BLA 761322

BLA APPROVAL

Sandoz, Inc.
Attention: Lisa Perkins, MBA
Associate Director
Regulatory Affairs, Biopharmaceuticals
100 College Road West
Princeton, NJ 08540

Dear Lisa Perkins:

Please refer to your biologics license application (BLA) dated and received May 24, 2022, and your amendments, submitted under section 351(k) of the Public Health Service Act for Tyruko (natalizumab-sztn) injection.

We acknowledge receipt of your major amendment dated February 17, 2023, which extended the goal date by three months.

LICENSING

We have approved your BLA for Tyruko (natalizumab-sztn) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Tyruko under your existing Department of Health and Human Services U.S. License No. 2003. Tyruko is indicated for the following indications:

1) Multiple Sclerosis (MS): Tyruko is indicated as monotherapy for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Natalizumab products increase the risk of PML. When initiating and continuing treatment with Tyruko, physicians should consider whether the expected benefit of Tyruko is sufficient to offset this risk.

2) Crohn's Disease (CD): Tyruko is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α.

   Important Limitations:
   In CD, Tyruko should not be used in combination with immunosuppressants or inhibitors of TNF-α.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture natalizumab-sztn drug substance at [redacted]. The final formulated drug product will be manufactured, filled, labeled, and packaged at [redacted]. You may label your product with the proprietary name, Tyruko, and market it in a 300 mg/15 mL injection in a single-dose vial.

DATING PERIOD

The dating period for Tyruko shall be 24 months from the date of manufacture when stored at 2°C to 8°C, protected from light. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be [redacted] from the date of manufacture when stored at [redacted]

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Tyruko to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Tyruko, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide). 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 (October 2009)*.[2]

The SPL will be accessible via publicly available labeling repositories.

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

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on April 20, 2023, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761322."** Approval of this submission by FDA is not required before the labeling is used.

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.

[1] See 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 at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Multiple Sclerosis

At this time we have determined that, with respect to multiple sclerosis, no pediatric studies will be required under PREA for your BLA.

Crohn's Disease

At this time we have determined that, with respect to Crohn's Disease, no pediatric studies will be required under PREA for your BLA.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Food Drug Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Tyruko to ensure the benefits of the drug outweigh the risk of progressive multifocal leukoencephalopathy (PML).

Your proposed REMS must also include the following:

Medication Guide: In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Tyruko poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Tyruko. FDA has determined that Tyruko is a product for which patient labeling could help prevent serious adverse effects and that has serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use, Tyruko. Under section 505-1 of the FDCA, FDA has also determined that a Medication Guide is necessary to ensure the benefits of the drug outweigh the risk of PML.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Tyruko.

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that Tyruko can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of PML listed in the labeling of the drug.

Your REMS includes the following elements to mitigate this risk:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions
- Each patient using the drug is subject to certain monitoring

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on May 24, 2022, 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.

Your REMS must be fully operational before you introduce Tyruko into interstate commerce.

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

Program Implementation and Operations

1. Program Implementation (for the first REMS assessment only)
    a. Date of Tyruko REMS launch
    b. Date when the REMS website became live and fully operational
    c. Date(s) when healthcare professionals, patients, infusion sites, and pharmacies could become certified/enrolled into the Tyruko REMS
    d. Date when distributors/wholesalers were authorized to distribute the drug (i.e., first order placed)
    e. Date when Tyruko REMS Program materials became available on the REMS Website and via the Contact Center
    f. Date when the REMS Contact Center was established and fully operational
    g. Date of first commercial distribution of Tyruko

2. Tyruko REMS Program Certification and Enrollment Statistics (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 and contracted outpatient pharmacies
g. Newly certified and active certified infusion sites

3. Shared Database Platform (provide 2 previous, current, and cumulative reporting periods)
    a. Documentation of prior natalizumab product 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 product history with a diagnosis of PML
        iv. Number of matched patients with CD and prior natalizumab product history with a diagnosis of PML
    b. Number of unique patients of all active patients that switched natalizumab products including:
        i. The number of times the unique patients switched between products

4. Infrastructure and Performance (provide 2 previous, current, and cumulative reporting periods)
    a. REMS Contact Center
        i. Number of calls received by the REMS contact center, stratified by stakeholder type and reason for the call
        ii. Summary of frequently asked questions (FAQ) by stakeholder type
        iii. Summary report of REMS-related problems identified and resulting corrective actions
        iv. Summary report of database-related problems identified and resulting corrective actions
        v. A description of each call, including stakeholder type and reason for the call, that may indicate an issue with access or burden (e.g., any identified burden or access issues associated with the shared database)
            a) Provide a detailed summary of any actions taken for the identified issue (e.g. corrective action plan, process improvement measure)
    b. REMS Website
        i. The number of visits and unique visits to the REMS website
        ii. The number of REMS materials downloaded and printed for each material

5. REMS Program Compliance (provide 2 previous, current, and cumulative reporting periods)
    a. Number of patients not enrolled into the Tyruko REMS but who were administered Tyruko [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 Tyruko 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. The number of notifications coming from infusion sites confirming patients switching back to Tyruko received from other natalizumab product REMS stratified by:
        i. Method of communication e.g., fax or on-line via the Pre-Infusion Checklist
    d. 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)
    e. A summary report of non-compliance identified, associated corrective and preventive action (CAPA) plans, and the status of CAPA plans including, but not limited to:
        i. A copy of the non-compliance plan, including the criteria for noncompliance for prescribers, pharmacies and infusion sites and actions taken to address non-compliance for each case, and which events will lead to suspension or decertification from the REMS
        ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of non-compliance, report the following information:

a) The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
b) The source of the noncompliance data
c) The results of root cause analysis

iii. The action(s) taken in response to non-compliance

f. 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

g. Audits
   i. Summary of audit activities including but not limited to:
      a) A copy of the audit plan used for each audited stakeholder
      b) The number of audits expected, and the number of audits performed for each stakeholder
      c) The number and types of deficiencies noted
      d) A unique ID for each stakeholder that had deviations to track deviations by stakeholder over time
      e) Documentation of completion of training for relevant staff
      f) A summary report of documented processes and procedures for complying with the REMS requirements
      g) Describe any corrective actions taken for any non-compliance identified during the audits as well as any preventative measures that were developed from uncovering these non-compliance events
         1. For those with deficiencies noted, report the number that successfully completed a corrective and preventative action (CAPA) plan within one month of the audit
         2. For any that did not complete the CAPA within one month of the audit, describe additional actions taken

h. Shared Database
   i. The number of times real-time data sharing regarding natalizumab product-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

6. Documentation of Safe Use (provide 2 previous, current, and cumulative reporting periods)
    a. Duration of Tyruko 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 shared database platform, duration of natalizumab product (Tyruko 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

7. Progressive Multifocal Leukoencephalopathy (PML) (provide 2 previous, current, and cumulative reporting periods):
    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 United States incidence of PML stratified by the three known risk factors [duration of natalizumab product (Tyruko and other approved natalizumab products) exposure, anti-JCV antibody status, and history of prior immunosuppressant use]
    b. New cases of PML or death identified from submitted discontinuation forms
    c. New cases of PML or death reported in the Periodic Safety Update Report (PSUR)
    d. New cases of PML or death identified in a confirmed switch patient stratified by cumulative duration of natalizumab product treatment, anti-JCV antibody status, and history of prior immunosuppressant use

Knowledge

8. Knowledge, Attitude and Behavior survey data (starting with the 12-month assessment then annually)
    a. Prescribers' understanding of the safe use of Tyruko including approved indications, contraindications, and risk of PML
    b. Patients' understanding of the risk of PML associated with Tyruko

c. Infusion site healthcare provider knowledge and behavior regarding Tyruko use, such as patient selection and checking the Pre-infusion Patient Checklist prior to each infusion

Overall Assessment of REMS Effectiveness

9. 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.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

i. Submit your proposed audit plan and non-compliance plan for FDA review within 60 days of this letter.

ii. Submit your proposed protocol for the knowledge surveys for FDA review within 90 days of this letter.

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 761322 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., **ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

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). 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, proposed 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 the 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 a REMS modification*, provide a rationale for why the REMS does not need to be modified.

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 761322 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761322/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761322/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761322/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 761322/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 REVISION FOR BLA 761322

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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance and enhanced pharmacovigilance for hypersensitivity events. Report all confirmed or possible cases of serious hypersensitivity events to the BLA in an expedited fashion as 15-day "alert reports" (described under 21 CFR 600.80(c)(1)), and include comprehensive summaries for all reported hypersensitivity events as part of your required postmarketing safety reports (e.g., periodic safety update reports [PSURs]). Your comprehensive summaries should include a dedicated assessment of all hypersensitivity events associated with transitioning between natalizumab products.

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]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80.

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of

[3] For the most recent version of a guidance, check the FDA guidance web page at https://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

the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

If you have any questions, call CDR Kristen Haslam, Regulatory Project Manager, at (240) 402-4246.

Sincerely,

{See appended electronic signature page}

Paul R. Lee, MD, PhD
Director
Division of Neurology 2
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/

PAUL R LEE
08/24/2023 03:30:47 PM