XCENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761411Orig1s000

Trade Name:	**NIKTIMVO injection, for intravenous use**
Generic or Proper Name:	**(axatilimab-csfr)**
Sponsor:	**Incyte Corporation**
Approval Date:	**August 14, 2024**
Indication:	**NIKTIMVO is a colony stimulating factor-1 receptor (CSF-1R)-blocking antibody indicated for the treatment of chronic graft-versus-host disease (cGVHD) after failure of at least two prior lines of systemic therapy in adult and pediatric patients weighing at least 40 kg.**

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

BLA 761411

BLA APPROVAL

Incyte Corporation
Attention: Lori Chlysta
Associate Director, Global Regulatory Affairs
1801 Augustine Cut-Off
Wilmington, DE 19803

Dear Lori Chlysta:

Please refer to your biologics license application (BLA) dated December 28, 2023, received December 28, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for NIKTIMVO (axatilimab-csfr) injection, for intravenous use.

LICENSING

We have approved your BLA for NIKTIMVO (axatilimab-csfr) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, NIKTIMVO under your existing Department of Health and Human Services U.S. License No. 2228. NIKTIMVO is indicated for the treatment of chronic graft-versus-host disease (cGVHD) after failure of at least two prior lines of systemic therapy in adult and pediatric patients weighing at least 40 kg.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture axatilimab-csfr drug substance at (b) (4) The final formulated drug product will be manufactured and filled at (b) (4), (b) (4) The filled drug product will be labeled and packaged at (b) (4) You may label your product with the proprietary name, NIKTIMVO, and market it as 50 mg/1 mL (50 mg/mL) injection in a single-dose vial.

DATING PERIOD

The dating period for NIKTIMVO shall be 24 months from the date of manufacture when stored at 5 ± 3 °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 (b) (4) months from the date of manufacture when stored at (b) (4) °C (b) (4)

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 NIKTIMVO 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 NIKTIMVO, 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.

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 Patient Package). 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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on June 18, 2024, 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**

[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.

and Container Labeling for approved BLA 761411." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for NIKTIMVO was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of infusion-related reactions and to assess signals of the serious risks of hepatotoxicity, pancreatitis, myositis, bone or growth disorders, and infections with longer duration of administration.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4669-1 Conduct a study to further characterize the nature, incidence, and severity of the known serious risk of infusion-related reactions (IRR) in at least 50

patients treated with at least 4 doses of axatilimab. The safety evaluation should include vital sign monitoring (temperature, pulse, respiratory rate, blood pressure, and oxygen saturation) at minimum immediately before initiation of the infusion; at 15 minutes, 30 minutes, and at the end of the infusion; and for a prescribed period post-infusion. Characterize changes in vital signs, anaphylaxis, respiratory distress, chills, back pain, flushing, chest-tightness, nausea, vomiting, and any other relevant signs or symptoms of IRR, as well as infusion interruptions and details regarding re-challenge (rate, time after initial interruption, outcome), if applicable. Collect details regarding medications used as pretreatment to prevent infusion-related reactions and medications used to alleviate infusion-related reactions.

The timetable you submitted on July 30, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2024
Final Protocol Submission:	06/2025
Trial Completion:	06/2027
Final Report Submission:	02/2028

Submit a summary of the analysis and datasets with the final report.

4669-2 Complete Study SNDX-6352-0504 and follow patients until all have completed 5 years of follow-up or discontinued earlier, to further characterize and determine the long-term effects of axatilimab on liver enzymes, lipase, creatine kinase, bone homeostasis, and infections that may develop or not subside due to prolonged exposure to axatilimab, to assess the potential serious risks of hepatoxicity, pancreatitis, myositis, bone or growth disorders, and infections, in these patients with cGvHD. Include sufficient bone monitoring, including but not limited to serial assessments of bone mineral density, markers of bone formation and bone resorption, and calcium and phosphate levels. Include incidence rates of each adverse event, risk factors, time to onset, and outcomes.

The timetable you submitted on July 30, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2024
Final Protocol Submission:	06/2025
Trial Completion:	12/2027
Final Report Submission:	08/2028

Submit the datasets with the final report.

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 139019 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4669-3 Perform a real-time commercial container closure system leachate study for the axatilimab drug product using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at regular intervals through the end of shelf life. The study results will be updated annually in the BLA Annual Report. The final results of this study and the toxicology risk evaluation for the levels of leachates detected in the drug product will be provided in the final study report to the BLA.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

The timetable you submitted on July 25, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 10/2030

4669-4 Perform a real-world shipping validation study for axatilimab drug product shipped through the actual commercial shipping lanes. The study will be performed under worst-case commercial shipping conditions and include the evaluation of axatilimab biochemical quality attributes from samples collected prior to and after shipment. The real-world shipping validation study design and results will be submitted in the final report to the BLA.

The timetable you submitted on July 25, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 10/2026

4669-5 Establish a two-tiered cell bank system for axatilimab by qualifying a working cell bank (WCB) lot that will be used for commercial drug substance manufacturing. The final WCB qualification study report will be submitted as a Prior Approval Supplement to the BLA.

The timetable you submitted on July 25, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2026

4669-6 Re-evaluate the proposed CSF-1R blockade bioassay lot release and stability acceptance criterion for axatilimab drug substance (DS) and drug product (DP) based on data generated from sample retains from all available axatilimab DS and DP lots used to support clinical development. The analysis of sample retains using the CSF-1R blockade bioassay and proposed revisions to the lot release and stability acceptance criterion will be submitted as a Prior Approval Supplement to the BLA.

The timetable you submitted on July 25, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2025

Submit clinical protocols to your IND 139019 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report

submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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*.[4]

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.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

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

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

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

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Thomas J. Meckley, Regulatory Project Manager, at 240-402-0566 or thomas.meckley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Acting Supervisory Associate Director
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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/

MARC R THEORET
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