BLA 761244

BLA APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Christopher Dougherty, PhD, MS
Director, Regulatory Affairs
900 Ridgebury Rd.
Ridgefield, CT 06877

Dear Dr. Dougherty:

Please refer to your biologics license application (BLA) dated and received October 1, 2021, and your amendments, submitted under section 351(a) of the Public Health Service Act for Spevigo (spesolimab-sbzo) intravenous injection.

We acknowledge receipt of your major amendment dated April 25, 2022, which extended the goal date by three months.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2006 to Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Spevigo (spesolimab-sbzo). Spevigo is indicated for the treatment of generalized pustular psoriasis flares in adults.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture spesolimab-sbzo drug substance at Boehringer Ingelheim Pharma GmbH & Co. KG in Biberach an der Riss, Germany. The final formulated drug product will be manufactured, filled, labeled, and packaged at Boehringer Ingelheim Pharma GmbH & Co. KG in Biberach an der Riss, Germany. You may label your product with the proprietary name, Spevigo and market it in 450 mg in 7.5 mL (60 mg/mL) solution in a 10 mL vial for intravenous infusion.

DATING PERIOD

The dating period for Spevigo shall be 24 months from the date of manufacture when stored at 2 to 8 °C. 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 (b) (4)

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Spevigo 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 Spevigo, 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. 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 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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to enclosed carton and container labeling, 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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed**

[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.

Carton and Container Labeling for approved BLA 761244." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Spevigo was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues in the intended population.

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 identify an unexpected serious risk of the effect of immunogenicity on the pharmacokinetics, safety, and efficacy on re-treatment of GPP flares that occur after the first flare has been treated and has resolved.

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.

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

4332-1 Conduct an open label safety trial to assess the effect of immunogenicity on pharmacokinetics (PK), safety, and efficacy on re-treatment of flares that occur after the first flare incidence has been treated and resolved.

The timetable you submitted on August 18, 2022, states that you will conduct this study according to the following schedule:

Final Protocol Submission: June 2, 2023
Trial Completion: February 10, 2028
Final Report Submission Date: April 27, 2028

4332-2 Submit the final reports with safety results from ongoing trials: 1) Effisayil-2 (clinicaltrials.gov identifier: NCT04399837, other study ID number: 1368-0027): Multi-center, Randomized, Parallel Group, Double Blind, Placebo Controlled, Phase IIb Dose-finding Study to Evaluate Efficacy and Safety of BI 655130 (Spesolimab) Compared to Placebo in Preventing Generalized Pustular Psoriasis (GPP) Flares in Patients With History of GPP, and 2) Effisayil-ON (clinicaltrials.gov identifier: NCT03886246, other study ID number: 1368-0025): An Open-label, Long Term Extension Study to Assess the Safety and Efficacy of BI 655130 Treatment in Patients With Generalized Pustular Psoriasis (GPP).

The timetable you submitted on August 18, 2022, states that you will submit final reports according to the following schedule:

Final Report Submission Date for Study 1368-0027: May 23, 2023
Final Report Submission Date for Study 1368-0025: September 8, 2028

4332-3 Submit the final report for the planned voluntary European Post-Authorization Safety Study (PASS).

The timetable you submitted on August 18, 2022, states that you will submit the final report for this study according to the following schedule:

Final PASS Report Submission Date: September 30, 2029

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 131311 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final

[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.

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 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 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.

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.

[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

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:

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

We request that for a period of 3 years from the beginning of U.S. marketing of this BLA, you submit all reported occurrences of possible Guillain Barre Syndrome (GBS) with Spevigo (spesolimab-sbzo) injection as 15-day expedited reports and we request that you provide detailed analyses of these reports as part of your required periodic safety reports (i.e., the Periodic Adverse Experience Report [PAER] required under 21 CFR 600.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should include an assessment of the interval and cumulative adverse event reports for all reports of GBS in your post-market safety database; reports from IND, non-IND, and BLA studies; and the medical literature. The summary should include the report narrative or the manufacturer control number if submitted to the FDA Adverse Event Reporting System.

To assist in identifying reports of possible GBS, we are providing a suggested search strategy with the following MedDRA Preferred Terms that may indicate a possible case of GBS: *Acute polyneuropathy; Acute infective polyneuritis; Acute inflammatory demyelinating polyradiculoneuropathy; Cranial nerve disorder; Demyelination; Demyelinating polyneuropathy; Guillain Barre syndrome; Guillain-Barre syndrome; Hyporeflexia; Miller Fisher syndrome; Paralysis ascending; Peripheral sensory neuropathy; Syndrome Guillain-Barre; Subacute inflammatory demyelinating polyneuropathy;* and *Weakness.*

In addition, we request that for a period of 5 years from the beginning of U.S. marketing of this BLA in the U.S., you submit all reported occurrences of possible exposure to Spevigo (spesolimab-sbzo) injection in pregnant patients, patients who are lactating, and infants exposed through breastmilk or infants who were exposed while in utero as 15-day expedited reports and we request that you provide detailed analyses of these reports as part of your required periodic safety reports (i.e., the Periodic Adverse Experience Report [PAER] required under 21 CFR 600.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should include an assessment of the interval and cumulative adverse event reports for all reports of pregnancy and lactation exposure in your post-market safety database; reports from IND, non-IND, and BLA studies; and the medical literature. The summary should include:

1. The report narrative or the manufacturer control number if submitted to the FDA Adverse Event Reporting System
2. Total number of cases of each adverse event of interest by time period and cumulative since approval
3. Patient and pregnancy outcome
4. Infant outcome
5. Age (Mean, Range)
6. Indication for Spevigo (spesolimab-sbzo)
7. Dosage of Spevigo (spesolimab-sbzo)
8. Concurrent and past medical history, past surgical history, smoking status
9. Concomitant drugs [list all, including prescription and over-the-counter medications (indication, dosage), herbal, and illicit substances]
10. Duration exposure to Spevigo (spesolimab-sbzo) for pregnant patient, fetus, or infant
11. Action taken with Spevigo (spesolimab-sbzo)
12. Dechallenge, Rechallenge information

In addition to the summary and assessment in each periodic report for both GBS and adverse events in pregnant patients, provide the above data, including the respective manufacturer control number for each case, in .xlsx format. Every effort should be made to obtain thorough and complete follow-up of events related to the serious

adverse events of interest, including making every effort to obtain results from specialist consults, assessments, or evaluations of patients with any events related to the adverse events of interest. The clinical information collected in this manner will enhance the quality of adverse event reports submitted to FDA and facilitate our assessment of these reports.

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, call Jennifer Harmon, Regulatory Project Manager, at 240-402-4880.

Sincerely,

{See appended electronic signature page}

Julie G. Beitz, MD
Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

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/

JULIE G BEITZ
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