BLA 761113

BLA APPROVAL

Sanofi Aventis US LLC.
Attention: Kari Jeschke, MA
Senior Director
50 Binney St
Cambridge, MA 02142

Dear Ms. Jeschke:

Please refer to your biologics license application (BLA) dated April 30, 2019, received April 30, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for isatuximab-irfc, injection.

LICENSING

We have approved your BLA for SARCLISA (isatuximab-irfc) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, SARCLISA under your existing Department of Health and Human Services U.S. License No. 1752. SARCLISA is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture isatuximab-irfc drug substance at Sanofi Chimie in Vitry-sur-Seine cedex, France. The final formulated drug product will be manufactured, filled, labeled, and packaged at Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany. The final formulated drug product will be also labeled and packaged at (b) (4) You may label your product with the proprietary name, SARCLISA, and market it in a single-dose vial for 100 mg/5 mL injection and a single-dose vial for 500 mg/25 mL injection.

DATING PERIOD

The dating period for SARCLISA shall be 36 months from the date of manufacture when stored at 2°C - 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 at (b) (4) °C.

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug substance.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of SARCLISA 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 SARCLISA, or in the manufacturing facilities, will require the submission of information to your biologics license application 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, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling text for the Prescribing Information, Patient Package Insert. 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]"

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 November 26, 2019, 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

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

this submission "**Final Printed Carton and Container Labeling for approved BLA 761113**." 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.

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 signal of a serious risk of acute myeloid leukemia, myelodysplastic syndrome and other second primary malignancies in patients receiving isatuximab in combination with pomalidomide and dexamethasone.

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:

3782-1 Conduct long term safety monitoring of patients enrolled in study (ICARIA) titled; "A Phase 3 Randomized, Open-label, Multicenter Study Comparing Isatuximab (SAR650984) in Combination With Pomalidomide and Low-Dose Dexamethasone Versus Pomalidomide and Low-Dose Dexamethasone in Patients With Refractory or Relapsed and Refractory Multiple Myeloma", to determine the incidence of acute myeloid leukemia, myelodysplastic syndrome and other second primary malignancies in patients receiving isatuximab in combination with pomalidomide and dexamethasone and it's potential to have a detrimental impact on overall

survival. Include incidence rates, time to onset, predisposing factors, and outcomes with the final report.

The timetable you submitted on February 5 and 20, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2019 (completed)
Final Protocol Submission:	03/2020
Study Completion:	06/2021
Final Report Submission:	12/2021

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]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of infusion related reactions in patients that weigh greater than or equal to 100 kilograms.

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

3782-2 Submit the final interim report and datasets containing at least 40 patients enrolled on studies TCD13983 VRDI Part B, TCD15484, EMN 24, and EFC15992 supplemented by data from other studies with similar pre-medications, if required, to assess the frequency and severity of infusion-related reactions, occurrence of intravenous infusion interruptions, infusion rate reductions, and discontinuation during the first two infusions of isatuximab administered via the fixed-volume infusion method in patients weighing ≥100 kg compared to patients weighing <100 kg.

The timetable you submitted on February 5 and 20, 2020 states that you will conduct this trial according to the following schedule:

Final Report Submission: 09/2022

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]

[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.

Submit clinical protocols to your IND 103217 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3782-3 Submit the overall survival analysis and datasets with the final report for clinical trial (ICARIA) titled; “A Phase 3 Randomized, Open-label, Multicenter Study Comparing Isatuximab (SAR650984) in Combination With Pomalidomide and Low-Dose Dexamethasone Versus Pomalidomide and Low-Dose Dexamethasone in Patients With Refractory or Relapsed and Refractory Multiple Myeloma” to provide additional long term efficacy data that may inform product labeling.

The timetable you submitted on February 5 and 20, 2020, states that you will conduct this study according to the following schedule:

Draft Submission:	06/2019 (completed)
Final Protocol Submission:	03/2020
Trial Completion:	06/2021
Final Report Submission:	12/2021

3782-4 Develop a validated assay to detect interference of isatuximab to any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response (CR) in patients with multiple myeloma. Complete and submit the final report of the validation study, that may provide information to prescribers about the use of the assay to determine CR.

The timetable you submitted on February 5, and 20, 2020, states that you will conduct this study according to the following schedule:

510(k) Submission:	10/2020
Final Report Submission:	02/2021

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

We remind you of your postmarketing commitment:

3782-5 Complete a real-time leachables study using the final container closure system with isatuximab drug product for each presentation to identify any potential leachables in final isatuximab drug product at initial, 6, 12, 24 and 36 months under storage condition between 2˚C-8˚C.

Final Report Submission: 09/2021

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 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. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Patient Package Insert, 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] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (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 the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[7]

POST APPROVAL FEEDBACK MEETING

New molecular entities and 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.

[7] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

If you have any questions, call Kimberly Scott, Regulatory Project Manager, at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

- 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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