BLA 761169/S-003

SUPPLEMENT APPROVAL
NEW POSTMARKETING REQUIREMENT
FULFILLMENT OF POSTMARKETING REQUIREMENT/COMMITMENTS

Regeneron Pharmaceuticals, Inc.
Attention: Yunji Kim, PharmD
Senior Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Dr. Kim:

Please refer to your supplemental biologics license application (sBLA), dated and received April 30, 2021 and your amendments, submitted under section 351(a) of the Public Health Service Act for Inmazeb (atoltivimab, maftivimab, and odesivimab-ebgn) injection, for intravenous use.

This Prior Approval supplemental biologics application provides for updates to the US Prescribing Information (USPI):

- DOSAGE AND ADMINISTRATION, Preparation and Administration, and HOW SUPPLIED/STORAGE AND HANDLING sections were updated with information regarding diluted Inmazeb storage conditions.
- CLINICAL PHARMACOLOGY, Microbiology subsection was updated with information on mechanism of action, resistance, binding activity, and neutralization activity data.

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 with minor editorial revisions listed below and reflected in the enclosed labeling.

- Change of the revision date to reflect the action date of this supplemental BLA.

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 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]

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).

FULFILLMENT OF POSTMARKETING REQUIREMENT/COMMITMENTS

We have received your submissions dated April 30, 2021 (PMCs 3936-4 and 3936-10) and May 27, 2021 (PMR 3936-1) containing the final reports for the following post-marketing requirement and commitments listed in the October 14, 2020, approval letter:

PMR 3936-1	Conduct a phenotypic study to determine the impact on binding and antiviral activity against REGN-EB3, atoltivimab (REGN3470), odesivimab (REGN3471), and maftivimab (REGN3479) using lentivirus-based particles pseudotyped with Zaire ebolavirus (EBOV) glycoprotein (GP) containing these substitutions to determine shifts in susceptibility: I274M, W275L, G528R, I544T, H549R, N563T, and E564A.
PMC 3936-4	Conduct a study to define the precise epitopes of atoltivimab(REGN3470), odesivimab (REGN3471), and maftivimab (REGN3479)
PMC 3936-10	Provide microbial hold time data in a microbial challenge study to support the total in-use time (storage and infusion time) of diluted INMAZEB in 5% Dextrose Injection beyond 4-hours at ambient temperature. The study should be conducted for twice the worst

[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.

case in-use time and bracketing the drug product concentrations that would be administered to patients. The study should also be representative of the in-use conditions; for example, neonates may be kept at temperatures above 20-25°C during infusion and the higher temperatures should be simulated in the study supporting in use conditions Key changes made within the USPI will be outlined in this review. For more detailed information, reference the clinical review and CMC review and attached labeling.

We have reviewed your submissions and conclude that the above requirement and commitments were fulfilled.

We remind you that there are post-marketing requirement and post-marketing commitments listed in the October 14, 2020 approval letter that are still open.

POSTMARKETING REQUIREMENT 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.

Since Inmazeb (atoltivimab, maftivimab, and odesivimab-ebgn) was approved on October 14, 2020, we have become aware of amino acid substitutions in the epitopes of monoclonal antibodies in the REGN-EB3 cocktail (INMAZEB) that could lead to treatment failure, and result in serious risk of transmission of a resistant form of the Ebola virus. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

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 serious risk of emergence of Ebola virus resistance to INMAZEB.

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 this serious risk.

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

PMR 4280-01 Conduct a phenotypic study to determine the impact on binding and antiviral activity against REGN-EB3, atoltivimab (REGN3470), maftivimab (REGN3479), and odesivimab (REGN3471) using lentivirus-based particles pseudotyped with Zaire ebolavirus

(EBOV) glycoprotein (GP) containing these substitutions to determine shifts in susceptibility:

1. Maftivimab (REGN3479): A507S, A507T, I527T, F535L
2. Odesivimab (REGN3471): Q221K, L239S, G271E

The timetable you submitted on March 30, 2022 state that you will conduct this study according to the following schedule:

Final Report Submission: 02/2023

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]

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.

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 Alicia Moruf, PharmD, MPH, RAC-US, Regulatory Project Manager, at 301-796-3953.

[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.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antivirals
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information

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/

POONAM MISHRA
05/13/2022 01:35:52 PM
on behalf of Division Director