

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761097Orig1s000

Trade Name: LIBTAYO

Generic or Proper Name: cemiplimab-rwlc

Sponsor: Regeneron Pharmaceuticals, Inc.

Approval Date: September 28, 2018

Indication: For the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

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APPROVAL LETTER



BLA 761097

BLA APPROVAL

Regeneron Pharmaceuticals, Inc.
Attention: Laura Simpson, Ph.D.
Director, Regulatory Affairs
777 Old Saw Mill River Rd
Tarrytown, NY 10591

Dear Dr. Simpson:

Please refer to your Biologics License Application (BLA) dated February 28, 2018, received February 28, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for LIBTAYO (cemiplimab-rwlc) injection, for intravenous use.

LICENSING

We have approved your BLA for LIBTAYO (cemiplimab-rwlc) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, LIBTAYO under your existing Department of Health and Human Services U.S. License No. 1760. LIBTAYO is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture cemiplimab-rwlc drug substance (b) (4) at Regeneron Pharmaceuticals, Inc. in Rensselaer, NY. The final formulated drug product will be manufactured and filled at (b) (4). The filled drug product will be labeled and packaged at (b) (4). You may label your product with the proprietary name, LIBTAYO, and market it in the 250 mg/ 5 mL (50 mg/mL) and 350 mg/7 mL (50 mg/mL) dosage forms.

DATING PERIOD

The dating period for LIBTAYO shall be 18 months from the date of manufacture when stored at 2°C – 8°C (36°F to 46°F). 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)

FDA LOT RELEASE

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

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 [21 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for Prescribing Information and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved BLA 761097.**” Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for cemiplimab-rwlc was not referred to an FDA advisory committee because, this biologic is not a first in class approval, the safety profile is acceptable for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC

who are not candidates for curative surgery or curative radiation; and, the evaluation of the safety data did not raise significant safety or efficacy issues that were unexpected for a biologic of this class.

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.

We are waiving the pediatric studies requirement for this application because necessary studies are impossible or highly impracticable as metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC occurs mostly in adults.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3489-1 Submit the clinical trial report for Trial R2810-ONC-1540 (Groups 1, 2 and 3) that includes the final analysis of objective response rate and duration of response in patients with advanced cutaneous squamous cell carcinoma (CSCC) including patients with metastatic disease and patients with locally advanced CSCC who are not candidates for surgery or radiation. Trial R2810-ONC-1540 will enroll at least 150 patients including at least 75 patients with locally advanced CSCC. All patients will have the opportunity for at least 1.5 years of follow-up following completion of cemiplimab-rwlc treatment to further characterize the durability of responses in both subgroups.

The timetable you submitted on August 15, 2018, states that you will conduct this trial according to the following schedule:

Trial Completion:	12/31/19
Final Report Submission:	06/30/20

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

We remind you of your postmarketing commitments:

3489-2 Validate the worst-case capping and crimping parameters using the validated dye ingress container closure integrity test method described in the BLA. Include appropriate positive controls with breaches $\leq 20 \mu\text{m}$ in the validation study.

The timetable you submitted on July 24, 2018, states that you will conduct this study according to the following schedule:

Study Completion:	09/30/18
Final Report Submission:	10/31/18

Submit clinical protocols to your IND 127100 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final study 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 package insert 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 package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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:

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 4206
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 <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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, please notify the Regulatory Project Manager for this application within two weeks of receipt of this letter.

If you have any questions, please call Ms. Missiratch (Mimi) Biable, Lead Regulatory Health Project Manager, at (301) 796-0154.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
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/

RICHARD PAZDUR
09/28/2018