CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761097Orig1s003

Trade Name:	LIBTAYO
Generic or Proper Name:	cemiplimab-rwlc
Sponsor:	Regeneron Pharmaceuticals, Inc.
Approval Date:	November 10, 2020
Indication:	LIBTAYO is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

BLA 761097/S-3

SUPPLEMENT APPROVAL

Regeneron Pharmaceuticals, Incorporated
Attention: Laura Simpson, Ph.D.
Senior Director Regulatory Affairs Safety & Biometrics, US Oncology
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Simpson:

Please refer to your supplemental biologics license application (sBLA), dated and received April 3, 2019, and your amendments dated February 21, 2020, June 2, 2020, July 9, 2020, and August 13, 2020, October 14, 2020, and November 13, 2020, submitted under section 351(a) of the Public Health Service Act for Libtayo (cemiplimab-rwlc) injection.

We also refer to our February 11, 2019, supplement request proposing changes to the approved labeling for the DOSAGE AND ADMINISTRATION, Dose Modifications subsection and the WARNINGS AND PRECAUTIONS, Immune-mediated Adverse Reactions subsections of the U.S. prescribing information.

We further reference our January 24, 2020, labeling discussion correspondence, which also included our purpose and goal to harmonizing programmed death-ligand 1 (PD-L1) blocking antibodies and programmed cell death protein 1 (PD-1) blocking antibodies with respect to immune-mediated adverse reactions across all PDL1/PD1 antibody drug products.

This Prior Approval supplemental biologics application provides for revisions to the U.S. prescribing information and medication guide to improve the presentation of drug safety information regarding immune-mediated adverse reactions across all Food and Drug Administration (FDA) approved programmed death-ligand 1 and programmed cell death protein 1 blocking antibody labels. In addition, editorial and formatting changes were made throughout the U.S. package insert for consistency with current labeling practices.

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] that is identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide) 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 Biologic License Application, 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).

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 none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the

[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.

final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, 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]

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved Biologic License Application (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions you may contact Felicia Diggs, Safety Regulatory Project Manager, at (240) 402-4932 or via email at Felicia.diggs@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jefferey Summers, MD
Associate Director for Translational Sciences
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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

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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/

JEFFERY L SUMMERS
11/10/2020 03:52:56 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761097Orig1s003

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LIBTAYO safely and effectively. See full prescribing information for LIBTAYO.

LIBTAYO® (cemiplimab-rwlc) injection, for intravenous use
Initial U.S. Approval: 09/2018

RECENT MAJOR CHANGES

Dosage and Administration (2.2)	11/2020
Warnings and Precautions (5.1)	11/2020
Warnings and Precautions (5.3)	11/2020

INDICATIONS AND USAGE

LIBTAYO is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation. (1)

DOSAGE AND ADMINISTRATION

The recommended dosage of LIBTAYO is 350 mg as an intravenous infusion over 30 minutes every 3 weeks. (2.1)

DOSAGE FORMS AND STRENGTHS

Injection: 350 mg/7 mL (50 mg/mL) solution in a single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Immune-Mediated Adverse Reactions (5.1)
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immune-mediated nephritis and renal dysfunction, and solid organ transplant rejection.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue LIBTAYO based on the severity of reaction. (2.2)
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue based on severity of reaction. (2.2, 5.2)
- Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT): Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 20%) were fatigue, rash, diarrhea, musculoskeletal pain, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-877-542-8296 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LIBTAYO is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of LIBTAYO is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

2.2 Dosage Modifications for Adverse Reactions

No dose reduction for LIBTAYO is recommended. In general, withhold LIBTAYO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue LIBTAYO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for LIBTAYO for adverse reactions that require management different from these general guidelines are summarized in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity[a]**	**Dosage Modifications**
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold[b]
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold[b]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times the ULN	Withhold[b]
	AST or ALT increases to more than 8 times the ULN or Total bilirubin increases to more than 3 times the ULN	Permanently discontinue

Adverse Reaction	Severity[a]	Dosage Modifications
Hepatitis with tumor involvement of the liver[c]	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold[b]
	AST or ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grades 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[b]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold[b]
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3 or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[b]
	Grades 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

ALT=alanine aminotransferase, AST=aspartate aminotransferase, ULN=upper limit of normal, SJS=Stevens-Johnson Syndrome, TEN=toxic epidermal necrolysis, DRESS=Drug Rash with Eosinophilia and Systemic Symptoms

a. Based on National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0

b. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.
c. If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue LIBTAYO based on recommendations for hepatitis with no liver involvement.

2.3 Preparation and Administration

- Visually inspect for particulate matter and discoloration prior to administration. LIBTAYO is a clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles. Discard the vial if the solution is cloudy, discolored or contains extraneous particulate matter other than trace amounts of translucent to white particles.

Preparation

- Do not shake.
- Withdraw 7 mL from a vial and dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 1 mg/mL to 20 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard any unused medicinal product or waste material.

Storage of Infusion Solution

- Store at room temperature up to 25°C (77°F) for no more than 8 hours from the time of preparation to the end of the infusion or at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation to the end of infusion.
- Allow the diluted solution to come to room temperature prior to administration.
- Do not freeze.

Administration

- Administer by intravenous infusion over 30 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron to 5-micron filter.

3 DOSAGE FORMS AND STRENGTHS

Injection: 350 mg/7 mL (50 mg/mL), clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

LIBTAYO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral

tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue LIBTAYO depending on severity *[see Dosage and Administration (2.2)]*. In general, if LIBTAYO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

LIBTAYO can cause immune-mediated pneumonitis. The definition of immune-mediated pneumonitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 3.7% (22/591) of patients receiving LIBTAYO, including fatal (0.3%), Grade 4 (0.3%), Grade 3 (1.0%), and Grade 2 (1.9%) adverse reactions. Pneumonitis led to permanent discontinuation of LIBTAYO in 1.9% of patients and withholding of LIBTAYO in 1.9% of the patients.

Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 59% of the 22 patients. Of the 11 patients in whom LIBTAYO was withheld for pneumonitis, 7 reinitiated LIBTAYO after symptom improvement; of these 1/7 (14%) had recurrence of pneumonitis.

Immune-Mediated Colitis

LIBTAYO can cause immune-mediated colitis. The definition of immune-mediated colitis included the required use of systemic corticosteroids or other immunosuppressants and the

absence of a clear alternate etiology. The primary component of the immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1 blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.
Immune-mediated colitis occurred in 1.2% (7/591) of patients receiving LIBTAYO, including Grade 3 (0.3%) and Grade 2 (0.7%) adverse reactions. Colitis led to permanent discontinuation of LIBTAYO in 0.2% of patients and withholding of LIBTAYO in 0.7% of patients.

Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 71% of the 7 patients. Of the 4 patients in whom LIBTAYO was withheld for colitis, none reinitiated LIBTAYO.

Immune-Mediated Hepatitis

LIBTAYO can cause immune-mediated hepatitis. The definition of immune-mediated hepatitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology.

Immune-mediated hepatitis occurred in 1.9% (11/591) of patients receiving LIBTAYO, including fatal (0.2%), Grade 4 (0.2%), and Grade 3 (1.5%) adverse reactions. Hepatitis led to permanent discontinuation of LIBTAYO in 0.8% of patients and withholding of LIBTAYO in 0.8% of patients.

Systemic corticosteroids were required in all patients with hepatitis. Nine percent (9%) of these patients (1/11) required additional immunosuppression with mycophenolate. Hepatitis resolved in 64% of the 11 patients. Of the 5 patients in whom LIBTAYO was withheld for hepatitis, none reinitiated LIBTAYO.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity *[see Dosage and Administration (2.2)]*.

Adrenal insufficiency occurred in 0.5% (3/591) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.3%) adverse reactions. No patient discontinued LIBTAYO due to adrenal insufficiency. LIBTAYO was not withheld in any patient due to adrenal insufficiency.

Hypophysitis

LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity *[see Dosage and Administration (2.2)]*.

Hypophysitis occurred in 0.2% (1/591) of patients receiving LIBTAYO, which consisted of 1 patient with Grade 3 hypophysitis.

Thyroid Disorders

LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity *[see Dosage and Administration (2.2)]*.

Thyroiditis: A single case of Grade 1 thyroiditis was observed in 591 patients receiving LIBTAYO in clinical trials.

Hyperthyroidism: Hyperthyroidism occurred in 1.9% (11/591) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.5%) adverse reactions. No patient discontinued treatment due to hyperthyroidism. Hyperthyroidism led to withholding of LIBTAYO in 0.3% of patients.

Systemic corticosteroids were required in 9% (1/11) of patients. Hyperthyroidism resolved in 46% of the 11 patients.

Hypothyroidism: Hypothyroidism occurred in 7% (42/591) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (6%) adverse reactions. No patient discontinued due to hypothyroidism. Hypothyroidism led to withholding of LIBTAYO in 0.3% of patients.

Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 7% of the 42 patients. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

Of the 2 patients in whom LIBTAYO was withheld for hypothyroidism, both reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy; the other did not experience recurrence of hypothyroidism.

Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis.

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold LIBTAYO depending on severity *[see Dosage and Administration (2.2)]*.

Type 1 diabetes mellitus occurred in 0.7% (4/591) of patients, including Grade 4 (0.5%) and Grade 3 (0.2%) adverse reactions. Type 1 diabetes mellitus led to permanent discontinuation of LIBTAYO in 0.2% of patients and withholding of LIBTAYO in 0.3% of patients.

Of the 2 patients in whom LIBTAYO was withheld for Type 1 diabetes mellitus, both reinitiated LIBTAYO and required insulin treatment.

Immune-Mediated Nephritis with Renal Dysfunction

LIBTAYO can cause immune-mediated nephritis. The definition of immune-mediated nephritis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology.

Immune-mediated nephritis occurred in 0.5% (3/591) patients receiving LIBTAYO, including Grade 3 (0.3%) and Grade 2 (0.2%) adverse reactions. Nephritis led to permanent discontinuation of LIBTAYO in 0.2% of patients and withholding of LIBTAYO in 0.3% of patients.

Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in all 3 patients. Of the 2 patients in whom LIBTAYO was withheld for nephritis, none reinitiated LIBTAYO.

Immune-Mediated Dermatologic Adverse Reactions

LIBTAYO can cause immune-mediated rash or dermatitis. The definition of immune-mediated dermatologic adverse reaction included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue LIBTAYO depending on severity *[see Dosage and Administration (2.2)]*.

Immune-mediated dermatologic adverse reactions occurred in 2.0% (12/591) of patients receiving LIBTAYO, including Grade 3 (1.0%) and Grade 2 (0.8%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of LIBTAYO in 0.3% of patients and withholding of LIBTAYO in 1.4% of patients.

Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 42% of the 12 patients. Of the 8 patients in whom LIBTAYO was withheld for dermatologic adverse reaction, 5 reinitiated LIBTAYO after symptom improvement; of these 60% (3/5) had recurrence of the dermatologic adverse reaction.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% in 591 patients who received LIBTAYO or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome / myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica

Endocrine: Hypoparathyroidism

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

5.2 Infusion-Related Reactions

Severe infusion-related reactions (Grade 3) occurred in 0.2% of patients receiving LIBTAYO. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction *[see Dosage and Administration (2.2)]*.

5.3 Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling.

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*
- Complications of Allogeneic HSCT *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in Warnings and Precautions reflect exposure to LIBTAYO in 591 patients in two open-label, single-arm, multicohort studies (Study 1423 and Study 1540), including 131 patients with mCSCC (nodal or distant), 88 patients with locally advanced CSCC, and 372 patients with other advanced solid tumors. LIBTAYO as a single agent or in combination with chemotherapy or radiation was administered intravenously at doses of 1 mg/kg every 2 weeks (n=27), 3 mg/kg every 2 weeks (n=470), 3 mg/kg every 3 weeks (n=12), 10 mg/kg every 2 weeks (n=6), 200 mg every 2 weeks (n=20) or 350 mg every 3 weeks (n=56). Among the 591 patients, 47% were exposed for ≥ 6 months and 27% were exposed for ≥ 12 months.

The data described below reflect exposure to LIBTAYO in 219 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540 *[see Clinical Studies (14)]*. Of these 219 patients, 131 had mCSCC (nodal or distant) and 88 had laCSCC. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=162) or 350 mg every 3 weeks (n=56) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 38 weeks (2 weeks to 110 weeks).

The safety population characteristics were: median age of 72 years (38 to 96 years), 83% male, 96% white, and European Cooperative Oncology Group (ECOG) performance score (PS) of 0 (44%) and 1 (56%).

The most common adverse reactions reported in at least 20% of patients were fatigue, rash, diarrhea, musculoskeletal pain, and nausea. The most common Grade 3-4 adverse reactions (≥ 2%) were cellulitis, anemia, hypertension, pneumonia, musculoskeletal pain, fatigue, pneumonitis, sepsis, skin infection, and hypercalcemia. LIBTAYO was permanently discontinued due to adverse reactions in 8% of patients; adverse reactions resulting in permanent discontinuation were pneumonitis, cough, pneumonia, encephalitis, aseptic meningitis, hepatitis, arthralgia, muscular weakness, neck pain, soft tissue necrosis, complex regional pain syndrome, lethargy, psoriasis, rash maculopapular, proctitis, and confusional state. Serious adverse reactions occurred in 35% of patients. Serious adverse reactions that occurred in at least 2% of patients were pneumonitis, cellulitis, sepsis, and pneumonia.

Table 2 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 3 summarizes Grade 3 or 4 laboratory abnormalities worsening from baseline in ≥ 1% of patients receiving LIBTAYO.

Table 2: Adverse Reactions in ≥ 10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

Adverse Reactions	**LIBTAYO N=219**	
	All Grades %	**Grades 3-4 %**
General and Administration Site		
Fatigue[a]	34	3
Skin and Subcutaneous Tissue		
Rash[b]	31	1

Pruritus[c]	18	0
Gastrointestinal		
Diarrhea[d]	25	0.5
Nausea	21	0
Constipation	13	0.5
Vomiting	10	0.5
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[e]	24	3
Arthralgia	11	1
Respiratory		
Cough[f]	14	0
Hematology		
Anemia	11	4
Endocrine		
Hypothyroidism	10	0
Metabolism and Nutrition		
Decreased appetite	10	0

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03

a. Fatigue is a composite term that includes fatigue and asthenia
b. Rash is a composite term that includes rash, rash maculopapular, erythema, dermatitis, dermatitis bullous, rash generalized, pemphigoid, rash erythematous, rash macular, rash pruritic, drug eruption, psoriasis, and skin reaction
c. Pruritus is a composite term that includes pruritus and pruritus allergic
d. Diarrhea is a composite term that includes diarrhea and colitis
e. Musculoskeletal pain is a composite term that includes back pain, pain in extremity, myalgia, musculoskeletal pain, and neck pain
f. Cough is a composite term that includes cough and upper airway cough syndrome

Table 3: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥ 1% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

Laboratory Abnormality	**Grade 3-4 (%)[a]**
Chemistry	
Increased aspartate aminotransferase	2
Increased INR	2
Hematology	
Lymphopenia	9
Anemia	5
Electrolytes	
Hyponatremia	5
Hypophosphatemia	4

Hypercalcemia	2

Toxicity graded per NCI CTCAE v. 4.03

[a] Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cemiplimab-rwlc in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Anti-drug antibodies (ADA) were tested in 467 patients who received LIBTAYO. The incidence of cemiplimab-rwlc treatment-emergent ADAs was 1.1% using an electrochemiluminescent (ECL) bridging immunoassay; 0.2% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death *(see Data)*. Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO *[see Use in Specific Populations (8.1)]*.

Contraception

LIBTAYO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of LIBTAYO have not been established in pediatric patients.

8.5 Geriatric Use

Of the 219 mCSCC or laCSCC patients who received LIBTAYO in clinical studies, 34% were 65 years up to 75 years and 41% were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

11 DESCRIPTION

Cemiplimab-rwlc is a human programmed death receptor-1 (PD-1) blocking antibody. Cemiplimab-rwlc is a recombinant human IgG4 monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2. Cemiplimab-rwlc is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture. Cemiplimab-rwlc has an approximate molecular weight of 146 kDa.

LIBTAYO (cemiplimab-rwlc) injection for intravenous use is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution with a pH of 6. The solution may contain trace amounts of translucent to white particles.

Each vial contains 350 mg of cemiplimab-rwlc. Each mL contains cemiplimab-rwlc 50 mg, L-histidine (0.74 mg), L-histidine monohydrochloride monohydrate (1.1 mg), sucrose (50 mg), L-proline (15 mg), Polysorbate 80 (2 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binding of the PD-1 ligands PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

Cemiplimab-rwlc is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

12.3 Pharmacokinetics

Cemiplimab-rwlc pharmacokinetic data were collected in 548 patients with various solid tumors, including 178 patients with CSCC. The pharmacokinetics of cemiplimab-rwlc was linear and dose proportional in the dose range of 1 mg/kg to 10 mg/kg LIBTAYO administered intravenously every 2 weeks.

In patients with CSCC, cemiplimab-rwlc steady-state exposure at 350 mg every 3 weeks is comparable to the exposure at 3 mg/kg every 2 weeks. At 350 mg every 3 weeks, the mean cemiplimab-rwlc concentrations (coefficient of variation, CV%) at steady-state ranged between a minimum concentration of 63 mg/L (45%) and a maximum concentration of 151 mg/L (31%). Steady-state exposure is achieved after 4 months of treatment.

Distribution

The volume of distribution of cemiplimab-rwlc at steady state is 5.2 L (24%).

Elimination

Cemiplimab-rwlc clearance (CV%) after the first dose is 0.33 L/day (39%) and decreases over time by 36%, resulting in a steady-state clearance (CL_{ss}) (CV%) of 0.21 L/day (39%). The elimination half-life (CV%) at steady state is 19 days (38%).

Specific Populations

The following factors have no clinically important effect on the exposure of cemiplimab-rwlc: age (27 to 96 years), sex, body weight (31 to 172 kg), race (White, Black, Asian and other), cancer type, albumin level (22 to 48 g/L), renal function (creatinine clearance determined by Cockcroft-Gault 25 mL/min or greater) and hepatic function (total bilirubin 0.35 to 45 µmol/L). LIBTAYO has not been studied in patients with moderate or severe hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of cemiplimab-rwlc for carcinogenicity or genotoxicity.

In a 3-month repeat-dose toxicology study in sexually mature cynomolgus monkeys, there were no cemiplimab-rwlc-related effects on fertility parameters (menstrual cycle, semen analysis, or

testicular measurements) or in male or female reproductive organs at doses up to the highest dose tested, 50 mg/kg/week (approximately 5.5 to 25.5 times the human exposure based on AUC at the clinical dose of 350 mg once every 3 weeks).

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *M. tuberculosis*–infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

The efficacy of LIBTAYO in 219 patients with metastatic (nodal or distant) cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who were not candidates for curative surgery or curative radiation was evaluated in two open-label, multi-center, non-randomized, multicohort studies: Study 1423 (NCT02383212) and Study 1540 (NCT02760498). Both studies excluded patients with autoimmune disease that required systemic therapy with immunosuppressant agents within 5 years; history of solid organ transplant; prior treatment with anti–PD-1/PD-L1 blocking antibodies or other immune checkpoint inhibitor therapy; infection with HIV, hepatitis B or hepatitis C; or ECOG PS $\geq$ 2.

Patients received LIBTAYO 3 mg/kg intravenously every 2 weeks for up to 48 weeks in Study 1423 or up to 96 weeks in Study 1540. An additional cohort of patients in Study 1540 received 350 mg every 3 weeks for up to 54 weeks. Treatment continued until progression of disease, unacceptable toxicity, or completion of planned treatment. Tumor response assessments were performed every 8 or 9 weeks. The major efficacy outcome measures were confirmed objective response rate (ORR), defined as complete response (CR) plus partial response (PR) as assessed by independent central review (ICR), and ICR-assessed duration of response (DOR). For patients with mCSCC without externally visible target lesions, ORR was determined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1). For patients with externally visible target lesions (laCSCC and mCSCC), ORR was determined by a composite endpoint that integrated ICR assessments of radiologic data (RECIST 1.1) and digital medical photography (WHO criteria).

Study 1540

Among the 193 patients with advanced CSCC enrolled in Study 1540 who received LIBTAYO at either 3 mg/kg every 2 weeks or 350 mg every three weeks, 115 had mCSCC and 78 had laCSCC. The median age was 72 years (38 to 96 years); 83% were male; 97% were White; 45% had ECOG PS 0 and 55% had ECOG PS 1; 34% received at least one prior anti-cancer systemic therapy; 90% received prior cancer-related surgery; and 68% received prior radiotherapy. Among patients with mCSCC, 77% had distant metastases and 23% had only nodal metastases.

For the responding patients presented in Table 4 below, the median time to response was 1.9 months (range: 1.7 to 9.1 months).

Efficacy results in patients who received 3 mg/kg every 2 weeks are presented in Table 4.

Table 4: Efficacy Results for Study 1540: 3 mg/kg every 2 weeks

Efficacy Endpoints[a]	**Metastatic CSCC LIBTAYO 3 mg/kg every 2 weeks**	**Locally Advanced CSCC LIBTAYO 3 mg/kg every 2 weeks**	**Combined CSCC**
	N = 59	**N = 78**	**N = 137**
Confirmed Objective Response Rate (ORR)			
ORR (95% CI)	49% (36, 63)	44% (32, 55)	46% (37, 55)
Complete response (95% CI)[b]	17% (8, 29)	13% (6, 22)	15% (9, 22)
Partial response (95% CI)	32% (21, 46)	31% (21, 42)	31% (24, 40)
Duration of Response (DOR)			
Median DOR in months (Range)	NR (2.8 – 21.6+)	NR (1.9 – 24.2+)	NR (1.9 – 24.2+)
Patients with observed DOR ≥ 6 months, n (%)[c]	27 (93%)	23 (68%)	50 (79%)
Patients with observed DOR ≥ 12 months, n (%)[c]	22 (76%)	12 (35%)	34 (54%)

CI: confidence interval; NR: Not reached; +: Denotes ongoing at last assessment

a. Median duration of follow up: mCSCC: 16.5 months; laCSCC: 9.3 months; combined CSCC: 11.1 months
b. Only includes patients with complete healing of prior cutaneous involvement; laCSCC patients in Study 1540 required biopsy to confirm CR.
c. The numerator includes the number of patients whose observed DOR reached at least the specified times of 6 or 12 months. Patients who did not have the opportunity to reach the specified timepoint were included in the denominator only.

Study 1540: 350 mg every 3 weeks

In an additional cohort in Study 1540, 56 patients received cemiplimab-rwlc at a dose of 350 mg intravenously every 3 weeks for up to 54 weeks. With a median duration of follow-up of 8.0 months, the confirmed ORR was 41% (95% CI: 28, 55), and 65% of responders had a DOR ≥ 6 months.

Study 1423

Among 26 CSCC patients in Study 1423, 16 had mCSCC and 10 had laCSCC. The median age was 73 years (52 to 88 years); 81% of patients were male; 92% of patients were White; the ECOG PS was 0 (38%) and 1 (62%); 58% of patients had received at least 1 prior anti-cancer systemic therapy; 92% of patients had received prior cancer-related surgery and 81% had

received prior radiotherapy. One patient in the mCSCC group was dosed at 1 mg/kg. The rest received 3 mg/kg every 2 weeks.

With a median duration of follow-up of 13.3 months, the confirmed ORR was 50% (95% CI: 30, 70); all responses were PRs. The median time to response was 1.9 months (range: 1.7 to 7.3 months) and 85% of responders had a DOR ≥ 6 months.

16 HOW SUPPLIED/STORAGE AND HANDLING

LIBTAYO (cemiplimab-rwlc) injection is a clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles. It is supplied in a carton containing 1 single-dose vial of:

- 350 mg/7 mL (50 mg/mL) (NDC 61755-008-01)

Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Protect from light. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Advise patients that LIBTAYO can cause immune-mediated adverse reactions including the following *[see Warnings and Precautions (5.1)]*:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of pneumonitis, including new or worsening symptoms of cough, chest pain, or shortness of breath.
- Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of colitis, including diarrhea, blood or mucus in stools, or severe abdominal pain.
- Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, or type 1 diabetes mellitus.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.
- Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT or Solid Organ Transplant Rejection

Advise patients to contact their healthcare provider immediately if they develop signs or symptoms of post-allogeneic HSCT complications or of solid organ transplant rejection *[see Warnings and Precautions (5.1, 5.3)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential that LIBTAYO can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment and for at least 4 months after the last dose of LIBTAYO *[see Use in Specific Populations (8.3)]*.

Lactation

Advise female patients not to breastfeed while taking LIBTAYO and for at least 4 months after the last dose *[see Use in Specific Populations (8.2)]*.

REGENERON

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Marketed by:
Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591) and
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MEDICATION GUIDE
LIBTAYO® (Lib-TIE-oh)
(cemiplimab-rwlc)
injection

What is the most important information I should know about LIBTAYO?
LIBTAYO is a medicine that may treat a certain type of skin cancer by working with your immune system. LIBTAYO can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during treatment or even after your treatment has ended.

Call or see your healthcare provider right away if you develop any new or worse signs or symptoms, including:

Lung problems.

- cough
- shortness of breath
- chest pain

Intestinal problems.

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

Liver problems.

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach-area (abdomen)
- dark urine (tea colored)
- bleeding or bruising more easily than normal

Hormone gland problems.

- headache that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heartbeat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems.

- decrease in your amount of urine
- blood in your urine
- swelling of your ankles
- loss of appetite

Skin problems.

- rash
- itching
- skin blistering or peeling
- painful sores or ulcers in mouth or nose, throat, or genital area
- fever or flu-like symptoms
- swollen lymph nodes

Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with LIBTAYO. Call or see your healthcare provider right away for any new or worsening signs or symptoms which may include:

- Chest pain, irregular heartbeat, shortness of breath or swelling of ankles
- Confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- Double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- Persistent or severe muscle pain or weakness, muscle cramps

- Low red blood cells, bruising

Infusion reactions that can sometimes be severe. Signs and symptoms of infusion reactions may include:

- chills or shaking
- itching or rash
- flushing
- shortness of breath or wheezing
- dizziness
- feel like passing out
- fever
- back or neck pain
- facial swelling

Rejection of a transplanted organ. Your healthcare provider should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had.

Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with LIBTAYO. Your healthcare provider will monitor you for these complications.

Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during your treatment with LIBTAYO. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with LIBTAYO if you have severe side effects.

What is LIBTAYO?

LIBTAYO is a prescription medicine used to treat people with a type of skin cancer called cutaneous squamous cell carcinoma (CSCC) that has spread or cannot be cured by surgery or radiation.

It is not known if LIBTAYO is safe and effective in children.

Before you receive LIBTAYO, tell your healthcare provider about all your medical conditions, including if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. LIBTAYO can harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider will give you a pregnancy test before you start treatment with LIBTAYO.
  - You should use an effective method of birth control during your treatment and for at least 4 months after the last dose of LIBTAYO. Talk to your healthcare provider about birth control methods that you can use during this time.
  - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with LIBTAYO.
- are breastfeeding or plan to breastfeed. It is not known if LIBTAYO passes into your breast milk. Do not breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive LIBTAYO?

- Your healthcare provider will give you LIBTAYO into your vein through an intravenous (IV) line over 30 minutes.
- LIBTAYO is usually given every 3 weeks.
- Your healthcare provider will decide how many treatments you will need.
- Your healthcare provider will do blood tests to check you for side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of LIBTAYO?
LIBTAYO can cause serious side effects, including:

- **See "What is the most important information I should know about LIBTAYO?"**

The most common side effects of LIBTAYO include tiredness, rash, diarrhea, muscle or bone pain, and nausea. These are not all the possible side effects of LIBTAYO.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of LIBTAYO.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about LIBTAYO, talk with your healthcare provider. You can ask your healthcare provider for information about LIBTAYO that is written for health professionals.

What are the ingredients of LIBTAYO?
Active ingredient: cemiplimab-rwlc
Inactive ingredients: L-histidine, L-histidine monohydrochloride monohydrate, sucrose, L-proline, Polysorbate 80, and Water for Injection, USP.

Manufactured by: Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591-6707 U.S. License No. 1760
Marketed by: Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591) and sanofi-aventis U.S. LLC (Bridgewater, NJ 08807)
For more information, call 1-877-542-8296

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: November 2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761097Orig1s003

MEDICAL REVIEW(S)

Medical Officer Review of anti-PD1/L1 antibody drug Labeling Supplements AMENDED

BLA	Application Holder	Product	Supplement	Date of Original Submission
125514	Merck	Keytruda (pembrolizumab)	S48	08-27-2018 (SDN2094)
125554	Bristol-Meyers-Squibb	Opdivo (nivolumab)	S71	08-31-2018 (SDN 2647)
761034	Genentech	Tecentriq (atezolizumab)	S20	10-19-2018 (SDN 633)
761069	AstraZeneca	Imfinzi (durvalumab)	S12	08-31-2018 (SDN 467)
761049	EMD Serono	Bavencio (avelumab)	S5	08-31-2018 (SDN 192)
761097	Regeneron	Libtayo (cemiplimab)	S3	08-04-2019 (SDN 117)

Primary Reviewer: Margaret Thompson

I. RECOMMENDED REGULATORY ACTION

The clinical review team recommends approval of the changes to the label and medication guide for each of the listed BLAs. See the approval letters for final agreed upon changes to the USPI.

II. REGULATORY HISTORY

- On July 18, 2018, FDA requested the application holder for each of the approved PD1/L1 blocking agents submit draft labeling for the Prescribing Information (PI) and Medication Guide (MG) as a prior approval supplement, proposing changes to the DOSAGE AND ADMINISTRATION, Dose Modification subsection and WARNINGS AND PRECAUTIONS, Immune-mediated Adverse Reactions subsection in accordance with an FDA labeling template provided with the request letter. This request was made to:
    - Merck for Keytruda (pembrolizumab) under BLA 125514
    - Bristol-Meyer-Squibb for Opdivo (nivolumab) under BLA 125554
    - Genentech for Tecentriq (atezolizumab) under BLA 761034
    - AstraZeneca for Imfinzi (durvalumab) under BLA 761069
    - EMD Serono for Bavenvio (avelumab) under BLA 761049

- On February 11, 2019, FDA submitted a similar request to Regeneron for Libtayo (cemiplimab) which was first approved September 2018.

III. BACKGROUND AND DISCUSSION

Rationale

The purpose of the supplements is to harmonize, where appropriate and applicable based on data, the labels with respect to immune-mediated adverse reactions across all PD1/L1 blocking antibodies with the following goals:

1. Simplify the labels through recognition of the common pathophysiology underlying immune-mediated adverse reactions (imARs) caused by blocking the PD-1/PD-L1 pathway and replacement of redundant text included for each type of imARs with general text applying to all imARs.

2. Provide consistent advice in the labels with respect to dose modification, based on the totality of safety across the PD1/L1 blocking antibodies.

3. Increase safety by applying experience with rare but serious imARs from one PD1/L1 blocking antibody to all of these drugs.

4. Increase readability by utilizing a consistent set of data and format for all imARs across all the labels.

Key Elements

- Section 2.5 Dose Modifications

  Shared introductory text:

> No dose reduction for DRUG is recommended. In general, withhold DRUG for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue DRUG for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating (b) (4) steroids.
>
> Dosage modifications for DRUG for adverse reactions that require management different from these general guidelines are summarized in Table X.

  The following imARs, requiring guidelines different from the general guidelines noted above, are included in the DMT: pneumonitis, colitis, hepatitis with no tumor involvement of the liver, hepatitis with tumor involvement of the liver, endocrinopathies, nephritis with renal dysfunction, exfoliative dermatologic conditions, myocarditis, and neurological toxicities.

The DMT also included guidelines for infusion-related reactions under Other Adverse Reactions.

Recommendations for dose modifications for adverse reactions for combination therapy are placed in a separate DMT if guidelines different from monotherapy use are necessary.

- Section 5.1 Warnings and Precautions – Severe and Fatal Immune-Mediated Adverse Reactions

  Shared introductory text:

  > DRUG is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.
  >
  > Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting (b) (4) PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.
  >
  > Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor (b) (4) closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
  >
  > Withhold or permanently discontinue DRUG depending on severity [see Dosage and Administration (2.x)]. In general, if DRUG requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid (b) (4).
  >
  > Toxicity management guidelines for adverse reactions that do not necessarily require systemic (b) (4) steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

The following individual imARs are described as non-numbered subsections under 5.1: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies (adrenal insufficiency, hypophysitis, thyroid disorders thyroiditis, hyperthyroidism, hypothyroidism, type I Diabetes Mellitus), immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions.

The following DRUG specific information for each imAR is included in the label under its non-numbered subsection:

- General specification(s), where applicable, regarding how the imAR was defined.
- Overall frequency of the imAR and breakdown by grade (2,3, 4, and 5).
- Frequency of discontinuation and withholding of the drug due to the imAR.
- Percentage of patients with the imAR who required systemic corticosteroids.
- Percentage of patients in whom the imAR resolved.
- Number of patients who reinitiated the drug after withholding for the imAR after symptom improvement and the number of these patients who had a recurrence of the imAR.

The following imARs are included under "Other Immune-Mediated Adverse Reactions"

Cardiac/Vascular: Myocarditis, pericarditis**,** vasculitis.

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis.

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities (b) (4). Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada like syndrome, as this may require treatment with systemic (b) (4) steroids to reduce the risk of permanent vision loss.

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae including renal failure), arthritis, polymyalgia rheumatic.

Endocrine: Hypoparathyroidism.

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic

necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

Additional Labeling Conventions

- Information regarding median time to event was removed from all labels. Early or late onset IMARs were not uncommon. The confidence intervals around median time to onset for IMARs with low incidence rates were large and this data was considered of limited value to clinicians.

- For a specific imAR, information regarding a subset of patients, e.g., patients who have received prior chest radiation, is included only if the imAR frequency, severity, or other clinically important characteristic is substantively different in that particular patient population. As a general guide, a cutoff of 5% difference was utilized.

- For a specific imAR, information regarding its incidence when DRUG is part of a combination regimen is included only if the imAR frequency, severity, or other clinically important characteristic is substantively different. As a general guide, a cutoff of 5% difference was utilized; however, consideration was given across a number of factors that resulted in the inclusion of specific combination regimen differences that were less than 5%.

Additional Comments:

- In some cases, incidence by grade and/or rechallenge information was not adequately captured on the supporting clinical trials to allow reanalysis for the consistent reporting in the amended label. In these cases, every effort was made to derive the information from data that was collected.

- In some cases, information regarding specific endocrinopathies was not captured in the clinical trials. In these instances, endocrinopathies were pooled.

- Immune-mediated encephalitis and immune mediated neuropathies, which had their own subsections in previous labels, were not given their own subsection within Section 5.1 (imARs) in the revised labels due to their low frequencies of occurrence. These imARs were retained in the list of rare but serious imARS ("Other Immune-Mediated Adverse Reactions") that appears at the end of Section 5.1.

- A separate numbered section for "Complications of Allogenic Hematopoietic Stem Cell Transplant" was included under Section 5 for all labels.

Medicine Guide (MG)

The MGs were similarly harmonized to present consistent information across the PD1/L1 blocking antibody drugs MGs. All MGs include the same set of worsening signs or symptoms for the following organ/tissues: Lung problems, Intestinal problems, Liver problems, Hormone gland problems, Kidney problems, and Skin problems. The set of organ/tissues is based on the imARs that have a subsection in 5.1.

In addition, a common set of other signs and symptoms based on the list of "Other Immune-Mediated Adverse Reactions" from Section 5.1 was added to each MG. The following common text is included in all MGs for PD1/L1 blocking antibodies:

> Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with DRUG. Call or see your healthcare provider right away for any new or worsening signs or symptoms, which may include:
>
> - chest pain, irregular heartbeat, shortness of breath, swelling of ankles
> - confusion, sleepiness, memory problems, seizures, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
> - double vision, blurry vision, sensitivity to light, eye pain or redness, changes in eyesight
> - persistent or severe muscle pain or weakness, muscle cramps
> - low red blood cells, bruising

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/s/

MARGARET C THOMPSON
11/13/2020 12:46:55 PM

JEFFERY L SUMMERS
11/13/2020 01:56:27 PM

Medical Officer Review of anti-PD1/L1 antibody drug Labeling Supplements

BLA	Application Holder	Product	Supplement	Date of Original Submission
125514	Merck	Keytruda (pembrolizumab)	S48	08-27-2018 (SDN2094)
125554	Bristol-Meyers-Squibb	Opdivo (nivolumab)	S71	08-31-2018 (SDN 2647)
761034	Genentech	Tecentriq (atezolizumab)	S20	10-19-2018 (SDN 633)
761069	AstraZeneca	Imfinzi (durvalumab)	S12	08-31-2018 (SDN 467)
761049	EMD Serono	Bavencio (avelumab)	S5	08-31-2018 (SDN 192)
761097	Regeneron	Libtayo (cemiplimab)	S3	08-04-2019 (SDN 117)

Primary Reviewer: Margaret Thompson

I. RECOMMENDED REGULATORY ACTION

The clinical review team recommends approval of the changes to the label and medication guide for each of the listed BLAs. See the approval letters for final agreed upon changes to the USPI.

II. REGULATORY HISTORY

- On July 18, 2018, FDA requested the application holder for each of the approved PD1/L1 blocking agents submit draft labeling for the Prescribing Information (PI) and Medication Guide (MG) as a prior approval supplement, proposing changes to the DOSAGE AND ADMINISTRATION, Dose Modification subsection and WARNINGS AND PRECAUTIONS, Immune-mediated Adverse Reactions subsection in accordance with an FDA labeling template provided with the request letter. This request was made to:
    - Merck for Keytruda (pembrolizumab) under BLA 125514
    - Bristol-Meyer-Squibb for Opdivo (nivolumab) under BLA 125554
    - Genentech for Tecentriq (atezolizumab) under BLA 761034
    - AstraZeneca for Imfinzi (durvalumab) under BLA 761069
    - EMD Serono for Bavenvio (avelumab) under BLA 761049

- On February 11, 2019, FDA submitted a similar request to Regeneron for Libtayo (cemiplimab) which was first approved September 2018.

III. BACKGROUND AND DISCUSSION

Rationale

The purpose of the supplements is to harmonize, where appropriate and applicable based on data, the labels with respect to immune-mediated adverse reactions across all PD1/L1 blocking antibodies with the following goals:

1. Simplify the labels through recognition of the common pathophysiology underlying immune-mediated adverse reactions (imARs) caused by blocking the PD-1/PD-L1 pathway and replacement of redundant text included for each type of imARs with general text applying to all imARs.

2. Provide consistent advice in the labels with respect to dose modification, based on the totality of safety across the PD1/L1 blocking antibodies.

3. Increase safety by applying experience with rare but serious imARs from one PD1/L1 blocking antibody to all of these drugs.

4. Increase readability by utilizing a consistent set of data and format for all imARs across all the labels.

Key Elements

- Section 2.5 Dose Modifications

  Shared introductory text:

> No dose reduction for DRUG is recommended. In general, withhold DRUG for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue DRUG for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating (b) (4) steroids.
>
> Dosage modifications for DRUG for adverse reactions that require management different from these general guidelines are summarized in Table X.

  The following imARs, requiring guidelines different from the general guidelines noted above, are included in the DMT: pneumonitis, colitis, hepatitis with no tumor involvement of the liver, hepatitis with tumor involvement of the liver, endocrinopathies, nephritis with renal dysfunction, exfoliative dermatologic conditions, myocarditis, and neurological toxicities.

The DMT also included guidelines for infusion-related reactions under Other Adverse Reactions.

Recommendations for dose modifications for adverse reactions for combination therapy are placed in a separate DMT if guidelines different from monotherapy use are necessary.

- Section 5.1 Warnings and Precautions – Severe and Fatal Immune-Mediated Adverse Reactions

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/s/

MARGARET C THOMPSON
11/10/2020 12:58:13 PM

JEFFERY L SUMMERS
11/10/2020 02:14:37 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761097Orig1s003

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date: October 9, 2020

To: Felicia Diggs
Safety Regulatory Health Project Manager
Division of Oncology 2 (DO2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Ruth Mayrosh, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Lynn Panholzer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Emily Dvorsky, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Rachael Conklin, MS, RN
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name)	Application Type/Number/Supplement Number	Dosage Form and Route	Applicant
LIBTAYO (cemiplimab-rwlc)	BLA 761097/S-003	injection, for intravenous use	Regeneron Pharmaceuticals, Inc.
KEYTRUDA (pembrolizumab)	BLA 125514/S-048	• for injection, for intravenous use • injection, for intravenous use	Merck Sharp & Dohme Corp.
BAVENCIO (avelumab)	BLA 761049/S-005	injection, for intravenous use	EMD Serono
OPDIVO (nivolumab)	BLA 125554/S-071	injection, for intravenous use	Bristol-Myers Squibb
IMFINZI (durvalumab)	BLA 761069/S-012	injection, for intravenous use	AstraZeneca
TECENTRIQ (atezolizumab)	BLA 761034/S-020	injection, for intravenous use	Genentech
YERVOY (ipilimumab)	BLA 125377/S-119	injection, for intravenous use	Bristol-Myers Squibb

1 INTRODUCTION

On July 18, 2018, the Agency sent a Prior Approval Supplement (PAS) request to the Applicants listed above to update their Prescribing Information (PI) and Medication Guide (MG) for the PD-1/PD-L1 blocking antibodies to include revisions for the following sections:

- DOSAGE AND ADMINISTRATION, Dose Modification subsection
- WARNINGS AND PRECAUTIONS, Immune-Mediated Adverse Reactions subsections

The purpose of these supplements is to incorporate class-labeling changes that will harmonize the labeling with respect to immune-mediated adverse reactions across the approved PD-1/PD-L1 blocking antibodies products.

On October 17, 2018 and November 6, 2018, the Division of Oncology 2 (DO2) requested that DMPP and OPDP review the MGs for the above listed PD-1/PD-L1 blocking antibodies products. On September 8, 2020, DO2 sent an updated consult requesting review of the MGs for the PD1/PD-L1 blocking antibodies products.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 2 (DO2) on September 8, 2020 for DMPP and

OPDP to review the Applicant's proposed Medication Guides (MGs) for the PD1/PD-L1 blocking antibodies products.

2 MATERIAL REVIEWED

- Draft LIBTAYO (cemiplimab-rwlc) injection MG and Prescribing Information (PI) received on August 13, 2020, and received by DMPP and OPDP on September 8, 2020.
- Draft KEYTRUDA (pembrolizumab) for injection and injection MG and PI received on August 19, 2020, and received by DMPP and OPDP on September 8, 2020.
- Draft BAVENCIO (avelumab) injection MG and PI received on August 21, 2020, and received by DMPP and OPDP on September 8, 2020.
- Draft OPDIVO (nivolumab) injection MG and PI received on August 20, 2020, and received by DMPP and OPDP on September 8, 2020.
- Draft IMFINZI (durvalumab) injection MG and PI received on September 4, 2020, and received by DMPP and OPDP on September 8, 2020.
- Draft TECENTRIQ (atezolizumab) injection MG and PI received on August 27, 2020, and received by DMPP and OPDP on September 8, 2020.
- Draft YERVOY (ipilimumab) injection MG and PI received on August 20, 2020, and received by DMPP and OPDP on September 8, 2020.

3 REVIEW METHODS

In our collaborative review of the MGs we:

- simplified wording and clarified concepts where possible
- ensured that the MGs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MGs are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the MGs meet the Regulations as specified in 21 CFR 208.20
- ensured that the MGs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MGs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the MGs is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MGs.

Please let us know if you have any questions.

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/s/

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EMILY M DVORSKY
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BARBARA A FULLER
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 6, 2020

To: Felicia M. Diggs, Safety Regulatory Health Project Manager
Office of Oncologic Diseases (OOD)

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for LIBTAYO® (cemiplimab-rwlc) injection, for intravenous use

BLA: 761097/Supplement 003

In response to OOD's consult request dated August 14, 2020, OPDP has reviewed the proposed product labeling (PI) and Medication Guide (MG) for LIBTAYO® (cemiplimab-rwlc) injection, for intravenous use. This supplement (S-003) provides for changes in accordance with the template provided in the Agency's February 11, 2019 request for a Prior Approval Supplement (PAS).

OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from OOD on September 8, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the proposed MG will be completed, and comments on the proposed MG will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
10/06/2020 12:21:58 PM

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELING ASSESSMENT

Date of Assessment:	March 2, 2020
Assessor:	Scott Dallas, RPh, Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Jens Fricke, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research I
Application:	BLA 761097 Supplement 003
Applicant:	Regeneron Pharmaceuticals, Inc.
Submission Dates:	April 3, 2019 and February 21, 2020
Product:	Libtayo (cemiplimab-rwlc)
Dosage form:	injection
Strength and Container-Closure:	350 mg/7 mL (50 mg/mL) solution in a single-dose vial
Purpose of assessment:	The applicant submitted a labeling supplement with safety-related labeling changes in accordance with the template provided by the Agency. In addition, the applicant has proposed to include two sentences in the labeling to state the product lacks preservatives.
Recommendations:	The prescribing information is acceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labeling	A
Acceptable Labeling	B

DISCUSSION

We assessed the proposed labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labeling for consistency with recommended labeling practices.

The applicant submitted a labeling supplement with draft safety-related labeling changes. In addition, the applicant proposed to include two sentences in the Prescribing Information to state the product lacks preservatives. The sentences provide messaging consistent with the statement (No Preservatives) that appears on the approved carton labeling.

The applicant proposed [redacted] (b) (4)

(b) (4)

The applicant also proposed to include the sentence "(b) (4)" in the second paragraph of Section 11 Description. The applicant's proposal was acceptable.

CONCLUSION

The prescribing information submitted on February 21, 2020 was assessed and found to be acceptable (see Appendix B) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on April 3, 2019)
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APPENDIX B. Acceptable Labeling

- Prescribing Information (submitted on February 21, 2020)
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Scott Dallas

Digitally signed by Scott Dallas
Date: 3/03/2020 10:20:00AM
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Jens Fricke

Digitally signed by Jens Fricke
Date: 3/03/2020 10:26:32AM
GUID: 57d6a75701b1361db26ba4f78c02a5a9

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761097Orig1s003

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

BLA 761097/S-3

LABELING DISCUSSION COMMENTS

Regeneron Pharmaceuticals, Incorporated
Attention: Laura Simpson, Ph.D.
Senior Director Regulatory Affairs Safety & Biometrics, US Oncology
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Simpson:[1]

Please refer to your supplemental biologics license application (sBLA) dated and received April 3, 2019, submitted under section 351(a) of the Public Health Service Act for Libtayo (cemiplimab-rwlc) injection.

We received your October 14, 2020, proposed labeling submission to this application, and have proposed revisions that are included as enclosures. We request that you resubmit labeling that addresses these issues by **Tuesday, November 3, 2020**. If you agree to all edits, resubmit a clean version of the label as final with updates to the dates (11/2020) of the Recent Major Changes section of the Highlights of Prescribing Information and the "Revised" sections of the U.S. prescribing information (PI) and medication guide. Provide both the U.S. PI and Medication Guide as one document.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

[1] 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.
[2] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

If you have any questions, you may contact me at (240) 402-4932 or via email at Felicia.diggs@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Felicia M. Diggs, R.N., B.S.N., M.S.N.
Safety Regulatory Health Project Manager
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosures:
- Content of Labeling
- Medication Guide

21 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

FELICIA DIGGS
10/27/2020 05:05:20 PM

BLA 761097/S-3

LABELING DISCUSSION COMMENTS

Regeneron Pharmaceuticals, Incorporated
Attention: Laura Simpson, Ph.D.
Senior Director Regulatory Affairs Safety & Biometrics, US Oncology
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Simpson:[1]

Please refer to your supplemental biologics license application (sBLA) dated and received April 3, 2019, submitted under section 351(a) of the Public Health Service Act for Libtayo (cemiplimab-rwlc) injection.

We received your August 13, 2020, proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by **Wednesday, October 14, 2020**. The resubmitted labeling will be used for further labeling discussions. Please note, the medication guide is currently still under review and not provided with this submission.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

[1] 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.
[2] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

If you have any questions, you may contact me at (240) 402-4932 or via email at Felicia.diggs@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Felicia M. Diggs, R.N., B.S.N., M.S.N.
Safety Regulatory Health Project Manager
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosures:

- Content of Labeling

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/s/

FELICIA DIGGS
10/09/2020 09:40:37 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor) Felicia M. Diggs, Office of Oncologic Diseases, 240-402-4932

REQUEST DATE

09/8/2020

NDA/BLA NO.

125514 S48
761049 S5
125554 S71
761097 S3
761069 S12
761034 S20
125377 S119

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)

NAME OF DRUG

Pemrolizumab
Avelumab
Nivolumab
Cemipliamab
Durvalumab
Atezolizumab
ipilimumab

PRIORITY CONSIDERATION

Medium- high

CLASSIFICATION OF DRUG

PD1/LI blocking antibody

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)

4 weeks or sooner

Sponsor:

Merck Sharp & Dohme Corp; EMD Serono; Bristol-Myers Squibb; Regeneron; AstraZeneca; Genentech

PDUFA Date: multiple all have passed

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PATIENT PACKAGE INSERT (PPI)
☒ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☒ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission:

125514 S48
761049 S5
125554 S71
761097 S3
761069 S12
761034 S20
125377 S119

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS: In August 2018, FDA submitted a supplement request to each company with an approved PD1/L1 blocking antibody to submit draft labeling for DOSAGE AND ADMINISTRATION, Dose Modification subsection and WARNINGS AND PRECAUTIONS, Immune-mediated Adverse Reactions subsections in accordance with an enclosed labeling template. Similar request was also made to PD1/L1 blocking antibodies subsequently approved. The purpose of these supplements is to harmonize the labels with respect to immune-mediated adverse reactions across all PD1/L1 blocking antibodies. The goals of this project are:

1. Simplify the labels by recognizing the common pathophysiology underlying all immune-mediated adverse reactions (IMARs) and replacing redundant text included for each type of IMARs with general text applying to all IMARs.
2. Provide consistent advice in the labels with respect to dose modification and allow for the least conservative guidance for individual IMARs for which there is evidence of safety by leveraging experience from all the PD1/L1 blocking antibodies.
3. Increase safety by applying experience with rare but serious IMARs from one PD1/L1 antibody block drug to all of these drugs.
4. Increase readability by utilizing a consistent set of data and format for all IMARs across all the labels.

Filing/Planning Meeting: [Insert Date(s)] N/A

Mid-Cycle Meeting: [Insert Date] N/A

Labeling Meetings: [Insert Dates] N/A

Wrap-Up Meeting: [Insert Date] N/A

SIGNATURE OF REQUESTER
Felicia M. Diggs, SRPM

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ✓ eMAIL (BLAs Only) ✓ DARRTS

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/s/

FELICIA DIGGS
09/08/2020 03:12:19 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-OPDP-RPM	Felicia M. Diggs, Safety Regulatory Health Project Manager/Office of Oncologic Diseases/ 240-402-4932

REQUEST DATE:	IND NO.	BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
8/14/2020		761097 S3	U.S. PI labels and medguide

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Lybtayo (cemiplimab)	Medium-high	PD1/LI blocking antibody	4 weeks or sooner

NAME OF FIRM:	
Regeneron	PDUFA Date: October 3, 2019

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PRESCRIBING INFORMATION (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☒ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☒ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

For OSE USE ONLY
- ☐ REMS

EDR link to submission:
View submission in docuBridge

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: In August 2018, FDA submitted a supplement request to each company with an approved PD1/L1 blocking antibody to submit draft labeling for DOSAGE AND ADMINISTRATION, Dose Modification subsection and WARNINGS AND PRECAUTIONS, Immune-mediated Adverse Reactions subsections in accordance with an enclosed labeling template. Similar request was also made to PD1/L1 blocking antibodies subsequently approved. The purpose of these supplements is to harmonize the labels with respect to immune-mediated adverse reactions across all PD1/L1 blocking antibodies. The goals of this project are:

1. Simplify the labels by recognizing the common pathophysiology underlying all immune-mediated adverse reactions (IMARs) and replacing redundant text included for each type of IMARs with general text applying to all IMARs.
2. Provide consistent advice in the labels with respect to dose modification and allow for the least conservative guidance for individual IMARs for which there is evidence of safety by leveraging experience from all the PD1/L1 blocking antibodies.
3. Increase safety by applying experience with rare but serious IMARs from one PD1/L1 antibody block drug to all of these drugs.
4. Increase readability by utilizing a consistent set of data and format for all IMARs across all the labels.

Mid-Cycle Meeting: N/A
Labeling Meetings: N/A
Wrap-Up Meeting: N/A

SIGNATURE OF REQUESTER Felicia M. Diggs SRPM	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ✓ eMAIL ☐ HAND

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/s/

FELICIA DIGGS
08/14/2020 11:12:07 AM

BLA 761097/S-3

LABELING DISCUSSION COMMENTS

Regeneron Pharmaceuticals, Inc.
Attention: Laura Simpson PhD.
Senior Director
Regulatory Affairs Safety & Biometrics, US Oncology
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Simpson:[1]

Please refer to your supplemental biologics license application (sBLA) dated and received April 3, 2019, submitted under section 351(a) of the Public Health Service Act for Libtayo (cemiplimab-rwlc) Injection, for intravenous use.

We received your April 3, 2019 proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by Friday, February 21, 2020. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

[1] 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.
[2] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

In addition, we have included a document that outlines the purpose of the label changes and the labeling requirements.

If you have any questions, you may contact me at (240) 402-4932 or via email at Felicia.diggs@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Felicia M. Diggs, R.N., B.S.N., M.S.N.
Safety Regulatory Health Project Manager
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosures:
- Content of Labeling
- PD1/LI Blocking Antibody Label Harmonization

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/s/

FELICIA DIGGS
01/24/2020 02:06:41 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761097/S-03

PRIOR APPROVAL SUPPLEMENT - ACKNOWLEDGEMENT & FILING

Regeneron Pharmaceuticals, Inc.
Attention: Laura Simpson, Ph.D.
Senior Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Simpson:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

BLA SUPPLEMENT NUMBER: 761097/S-03

PRODUCT NAME: LIBTAYO (cemiplimab- rwlc) injection, for intravenous use

DATE OF SUBMISSION: April 3, 2019

DATE OF RECEIPT: April 3, 2019

This supplemental labeling application proposes to revise the DOSAGE AND ADMINISTRATION, Dose Modifications (2.11) subsection and the WARNINGS AND PRECAUTIONS, Immune-mediated Adverse Reactions subsections of the package insert in accordance with the February 11, 2019 Supplement Request Letter.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 3, 2019 in accordance with 21 CFR 601.2(a).

If the application is filed, the goal date will be October 3, 2019.

CONTENT OF LABELING

If you have not already done so, promptly submit the *content of labeling* [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeli/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

If you have questions, call me at (240) 402-3968.

Sincerely,

{See appended electronic signature page}

Karen Hennessy, CRNP
Safety Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KAREN A HENNESSY
06/11/2019 01:48:25 PM