CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761097Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761097
PDUFA Goal Date	October 28, 2018
OSE RCM #	2017-2592
Reviewer Name(s)	Joyce Weaver, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	July 27, 2018
Subject	Evaluation of Need for a REMS
Established Name	Cemiplimab
Trade Name	Libtayo
Name of Applicant	Regeneron
Therapeutic Class	Programmed cell death ligand 1 (PD-L1) blocking antibody
Formulation(s)	Injection
Dosing Regimen	350 mg intravenously every 3 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) cemiplimab is necessary to ensure the benefits outweigh its risks. Regeneron submitted a Biologics License Application (BLA 761097) for cemiplimab with the proposed indication the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma (CSCC) who are not candidates for surgery. The risks associated with cemiplimab include immune-(b) (4) pneumonitis, colitis, hepatitis, endocrinopathies, (b) (4) nephritis, infusion reactions, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

Should cemiplimab be approved, DRISK has concluded that a REMS is not needed to ensure its benefits outweigh its risks. The adverse events observed in clinical testing are consistent with those known to occur with this class of biologic products.

DRISK and the Division of Oncology Products 2 (DOP 2) agree that the safety profile for cemiplimab is acceptable for the patient population, and healthcare providers who will prescribe and administer cemiplimab are likely to be able to manage the cemiplimab-emergent adverse events without additional risk mitigation measures beyond labeling.

1 Introduction

This review by the DRISK evaluates whether a REMS for the NME cemiplimab is necessary to ensure the benefits outweigh its risks. Regeneron submitted BLA 761097 for cemiplimab with the proposed indication treatment of patients with metastatic CSCC or patients with locally advanced CSCC who are not candidates for surgery. This application is under review in DOP 2. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Cemiplimab, a new molecular entity[a], is a programmed death-1 (PD-1) blocking antibody that blocks the interaction between the PD-1 ligand and the PD-1 receptor found on T cells, thus enhancing the immune response against cancer cells. Cemiplimab is proposed for the treatment of patients with metastatic CSCC or patients with locally advanced CSCC who are not candidates for surgery.

Cemiplimab will be supplied as 250 mg/5 mL and 350 mg/7 mL vials. Cemiplimab will be administered as a 350 mg infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.[b]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Cemiplimab was granted breakthrough therapy designation (September 6, 2017) for the treatment of for the treatment of adults with metastatic CSCC and adults with locally advanced and unresectable CSCC.

Regeneron announced April 3, 2018 that the marketing authorization application for cemiplimab had been accepted for review by the European Medicines Agency (EMA). Cemiplimab is not approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761097 relevant to this review:

- 09/6/2017: breakthrough therapy designation granted
- 11/6/2017: rolling review granted
- 11/29/2017: Pre-BLA meeting; REMS not discussed
- 4/27/2018: Priority review granted; PDUFA 10/28/18
- 6/8/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference; the Division indicated that there were no major safety concerns identified and a REMS was likely not needed

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

CSCC is the second most common nonmelanoma skin cancer. The Rochester Epidemiology Project, conducted by the Mayo Clinic, showed an overall 263% increase in the incidence of CSCC between the 1976 to 1984 and 2000 to 2010 periods.[1,c] Rates are likely increasing with the aging of the U.S. population. In 2012 an estimated 5604 to 12,572 people with CSCC developed nodal metastases and 3932 to 8791 people died from CSCC. The incidence of CSCC is higher in the southern and central United States, and the mortality is comparable to melanoma.[2,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Most cases of CSCC are treated with surgery. The local recurrence rates are about 3% following Mohs surgery and 5% after standard surgical excision.[3] Less than 5% of patients with CSCC require nonsurgical treatment.[4] However, for those patients requiring nonsurgical treatment, good options are not available; there are no approved therapies, and there is no widely accepted standard of care for CSCC.

[c] Section 505-1 (a) of the FD&C Act*: FDAAA factor (A): The estimated size of the population likely to use the drug.*

[d] Section 505-1 (a) of the FD&C Act*: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

Platinum-based chemotherapy and epidermal growth factor receptor inhibitors have been used, but are not generally successful in managing disease, and result in considerable toxicity.[5]

4 Benefit Assessment[6,e]

The efficacy of cemiplimab was examined in a phase 2 single-arm open-label trial in patients with advanced CSCC (n=137).[7] Patients were treated with 350 mg cemiplimab every 3 weeks or 3 mg/kg cemiplimab every 2 weeks. The patients were mostly male (85%), elderly (70% 65 years of age or older) and white (97%).

The primary efficacy measure was objective response rate. The overall objective response rate was 47% (95% CI, 38, 57). The duration of response data were not mature at the time of cutoff of the data for submission of the application.

5 Risk Assessment & Safe-Use Conditions[8, f]

The safety database comprised data from 534 patients who had received cemiplimab.

The most important serious adverse reactions are immune (b) (4) pneumonitis, immune (b) (4) colitis immune (b) (4) hepatitis, immune- (b) (4) endocrinopathies, immune (b) (4) adverse reactions, immune (b) (4) nephritis, other immune (b) (4) adverse reactions, infusion-related reactions, and embryo-fetal toxicity.

5.1 IMMUNE (b) (4) PNEUMONITIS

Section 5.1 of the draft labeling describes the risk of immune (b) (4) pneumonitis requiring the use of corticosteroids. Pneumonitis occurred in 2.4% of patients (b) (4) (b) (4)

(b) (4) IMMUNE (b) (4) COLITIS

Section (b) (4) of the draft labeling describes the risk of immune- (b) (4) colitis. Colitis occurred in 0.9% of patients (b) (4)

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

(b) (4) IMMUNE (b) (4) HEPATITIS

Section (b) (4) of the draft labeling describes the risk of immune- (b) (4) hepatitis. Hepatitis occurred in 2.1% of patients (b) (4) .

(b) (4) IMMUNE (b) (4) ENDOCRINOPATHIES

Section (b) (4) of the draft labeling describes the risk of immune (b) (4) endocrinopathies. Endocrinopathies included hypothyroidism (6% of patients), hyperthyroidism (1.5%), hypophysitis (0.2%), adrenal insufficiency (0.4%), and type I diabetes (0.7%). (b) (4) .

(b) (4) IMMUNE (b) (4) SKIN ADVERSE REACTIONS

Section (b) (4) of the draft labeling describes the risk of immune-related skin adverse reactions. Skin adverse reactions occurred in 1.7% of patients (b) (4)

(b) (4) IMMUNE (b) (4) NEPHRITIS

Section (b) (4) of the draft labeling describes the risk of immune (b) (4) nephritis. Nephritis occurred in 0.6% of patients (b) (4)

(b) (4) OTHER IMMUNE- (b) (4) ADVERSE REACTIONS

(b) (4)

(b) (4)

INFUSION-RELATED REACTIONS

Section (b) (4) of the draft labeling describes infusion-related reactions. Grade 3 reactions occurred in 0.2% of patients (b) (4)

(b) (4)

EMBRYO-FETAL TOXICITY

(b) (4)

6 Expected Postmarket Use

Cemiplimab is likely to be used in healthcare settings capable of performing laboratory testing and administering intravenous infusions. Likely settings of use include hospitals, outpatient clinics, and oncology medical practices. The adverse events that presented in clinical testing with cemiplimab would not preclude the use of the cemiplimab in these settings. Health care personnel within these settings have the professional training to identify and manage the adverse events that presented in clinical testing.

The patient population likely to receive cemiplimab will be older patients (most patients clinical testing were in excess of 65 years of age) with metastatic CSCC or patients with locally advanced CSCC who are not candidates for surgery. Patients would be expected to be able to report their treatment-emergent signs and symptoms to their health care providers, and to undergo appropriate laboratory testing.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for cemiplimab.

8 Discussion of Need for a REMS

The Clinical Reviewer believes the data support a favorable benefit:risk assessment for cemiplimab for the treatment of patients with advanced CSCC based on the following:

- The effect size on durable response rate is larger than that reported with chemotherapy or EGFR inhibitors.
- Evidence of improvement in disfiguring cutaneous lesions.
- Unmet need.
- The main safety concerns are immune-related adverse events; these were consistent with other drugs in the class and are generally manageable.

The division has advised that the data do not support the need for a REMS because the risks associated with cemiplimab are known effects of the class of drugs, and are consistent in incidence and severity with other drugs in the class. The clinical reviewer agrees with the applicant that none of the adverse reactions warrant a boxed warning in the labeling.

DRISK recommends that, should cemiplimab be approved, a REMS is not needed to ensure its benefits outweigh its risks. The risks associated with cemiplimab are known effects of the class of drugs, and are consistent in incidence and severity with other drugs in the class. The healthcare community has experience with identifying and managing these adverse events. The other drugs in the class were approved without REMS.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits of cemiplimab outweigh its risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

[1] Muzic J. Incidence and Trends of Basal Cell Carcinoma and Cutaneous Squamous Cell Carcinoma. Mayo Clinic Proceedings: 92 (6): 890-898.

[2] Karia PS. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol. 2013 Jun;68(6):957-66. doi: 10.1016/j.jaad.2012.11.037. Epub 2013 Feb 1.

[3] Lansbury L et al. Interventions for non-metastatic squamous cell carcinoma of the skin: Systematic review and pooled analysis of observational studies. BMJ 2013 Nov 4; 347:f6153.

[4] Kauvar AN. Consensus for Nonmelanoma Skin Cancer Treatment, Part II: Squamous Cell Carcinoma, Including a Cost Analysis of Treatment Methods. Dermatol Surg 2015. Nov;41(11):1214-40.

[5] Kauvar AN. Consensus for Nonmelanoma Skin Cancer Treatment, Part II: Squamous Cell Carcinoma, Including a Cost Analysis of Treatment Methods. Dermatol Surg 2015. Nov;41(11):1214-40.

[6] Casey D. Efficacy data summarized from Clinical Reviewer's presentation at the Mid-cycle Team Review Meeting, May 24, 2018, and from the FDA-edited labeling as of July 10, 201 8.

[7] ClinicalTrials.gov Identifier: NCT02760498

[8] Casey D. Clinical presentation of BLA 761097 at mid-cycle meeting, May 24, 2018, and from the FDA-edited labeling as of July 10, 2018.

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/s/

ELIZABETH E EVERHART on behalf of JOYCE P WEAVER
07/27/2018

ELIZABETH E EVERHART
07/27/2018
I concur

CYNTHIA L LACIVITA
07/27/2018