REGENERON®

Public Summary of the Risk Management Plan (RMP)
LIBTAYO® (cemiplimab)

Marketing Autorization Holder: Regeneron Switzerland GmbH
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Disclaimer: The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP Summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Libtayo is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Libtayo in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Regeneron Switzerland GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Libtayo.

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for LIBTAYO® (cemiplimab)

This is a summary of the RMP for cemiplimab. The RMP details important risks of cemiplimab, how these risks can be minimised, and how more information will be obtained about cemiplimab risks and uncertainties (missing information).

Cemiplimab summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how cemiplimab should be used.

This summary of the RMP for cemiplimab should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR). *To be adapted locally.*

Important new concerns or changes to the current ones will be included in updates of cemiplimab RMP.

I. The Medicine and What it is Used For

Cemiplimab is authorised as monotherapy indicated for the treatment of adult patients with:

(1) Cutaneous Squamous Cell Carcinoma

LIBTAYO as monotherapy is indicated for the treatment of adult patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation.

(2) Basal Cell Carcinoma

LIBTAYO as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).

(3) Non-Small Cell Lung Cancer

LIBTAYO as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC who are not candidates for definitive chemoradiation, or
- metastatic NSCLC.

LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells) with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC who are not candidates for definitive chemoradiation or
- metastatic NSCLC.

(4) Cervical Cancer

LIBTAYO as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of cemiplimab, together with measures to minimise such risks and the proposed studies for learning more about cemiplimab's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

In the case of cemiplimab, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of cemiplimab is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of cemiplimab are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of cemiplimab. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information:

Important Identified Risks:

- Immune-mediated adverse reactions (imARs) such as immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin reactions, nephritis, and other imARs
- Infusion-related reactions (IRRs)

Important Potential Risks:

Lack of effect due to anti-drug antibodies (ADAs)

II.B Summary of Important Risks

Important Identified Risk: Immune-mediated Adverse Reactions	
Evidence for Linking the Risk to the Medicine	Cemiplimab Monotherapy: A total of 249 (20.8%) patients exposed to cemiplimab monotherapy in clinical trials experienced at least 1 imAE, including fatal or grade 5 (0.3%), life-threatening or grade 4 (0.6%), severe or grade 3 (5.6%), and moderate or grade 2 (11.2%). Fifty-six (4.7%) patients discontinued treatment due to imAEs. Cemiplimab in Combination Therapy (cemiplimab/chemotherapy): A total of 59 (18.9%) patients exposed to cemiplimab in combination therapy in clinical trials and included in the RMP experienced at least 1 imAE. Grade ≥3 imAEs were reported in 9 (2.9%) patients, including one patient (0.3%) with grade 5. Three (1.0%) patients discontinued treatment due to imAEs.
Risk Factors and Risk Groups	Patients with a history of or ongoing autoimmune disease may be at higher risk of developing imAEs and were excluded from the development programme for cemiplimab. Patients who were previously exposed to idelalisib may be at increased risk of experiencing severe immune-mediated mucocutaneous adverse reactions.
Risk Minimisation Measures	Routine risk communication messages: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.2 and 4.4 PL sections 2 and 3 Other routine risk minimisation measures beyond the Product Information: Legal status: Cemiplimab is subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of cancer. Additional risk minimisation measures: Patient Alert Card

Important Identified Risk: Infusion-related Reactions	
Evidence for Linking the Risk to the Medicine	Cemiplimab Monotherapy: In Study 1423, Study 1540, Study 1620, Study 1624 and Study 1676, IRRs occurred in patients receiving cemiplimab. These have also been observed in patients exposed to other PD-1 inhibitors. Infusion-related reactions occurred in 7.3% (87/1198) of patients receiving cemiplimab including 1 (<0.1%) patient with grade 3 IRRs. Infusion-related reactions led to permanent discontinuation of cemiplimab in 1 (<0.1%) patient. The most common symptoms of infusion-related reaction were nausea, pyrexia, and vomiting. All patients recovered from infusion-related reaction. Cemiplimab in Combination Therapy (cemiplimab/chemotherapy): Infusion-related reactions occurred in 2.2% (7/312) of patients receiving cemiplimab in combination therapy in clinical trials, all < grade 3. No IRRs led to permanent discontinuation of cemiplimab. The most common symptoms of infusion-related reaction were vomiting and pruritus. All patients recovered from infusion-related reaction.
Risk Factors and Risk Groups	Even though all patients are potentially at risk of IRRs, patients with documented allergic reactions or acute hypersensitivity reactions attributed to antibody treatments may be at higher risk of developing severe IRRs and were excluded from the development programme for cemiplimab.
Risk Minimisation Measures	Routine communication messages: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.2, 4.3, and 4.4. PL sections 2 and 3 Other routine risk minimisation measures beyond the Product Information: Legal status: Cemiplimab is subject to restricted medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer. Additional risk minimisation measures: Patient Alert Card
Additional pharmacovigilance activities	None

Important Potential Risks: Lack of Effect due to Anti-drug Antibodies	
Evidence for Linking the Risk to the Medicine	In nonclinical studies, the prevalence of immunogenicity/ADA was high; however, continuous exposure was maintained for 80% and 50% of animals throughout the 4-week and 26-week toxicology studies, respectively. As cemiplimab is a human antibody, the presence of ADA following cemiplimab administration to cynomolgus monkeys was expected and not considered predictive of the human ADA response to cemiplimab. In the overall population of patients with solid tumours, immunogenicity was assessed in all patients with solid tumours, including patients with NSCLC in Study 16113 Part 2, after cemiplimab administration as monotherapy (Studies 1423, 1540, 1620, 1624 and 1676) or in combination with radiotherapy and/or chemotherapy (Study 1423) or with chemotherapy (Study 16113 Part 2). The incidence of treatment-emergent ADA in all patients with solid tumours in the ADA analysis set (n=1310) was low (approximately 2.5%), including the subset of patients who received cemiplimab 350 mg Q3W. The ADA titers were generally low (< 1,000). Overall, only 3 patients (0.3%) had a persistent ADA response. No patients were positive for neutralizing antibodies (NAbs). The presence of treatment-emergent ADA did not appear to have a clinically meaningful effect on cemiplimab concentrations (Study 1423 Final CSR Appendix 5 [CP Report] Section 4.4, Study 1540 Interim CSR Appendix 5 [CP Report] Section 4.4, Study 1620 Interim CSR Appendix 5 [CP Report] Section 4.3, Study 1624 Primary Analysis CSR Appendix 16.1.15 [CP Report] Section 4.3, Study 1676 Primary Analysis CSR Appendix 16.1.15 [CP Report] Section 4.3 and Study 16113 Part 2 Primary Analysis CSR Appendix 16.1.15 [CP Report] Section 4.3).
Risk Factors and Risk Groups	Risk factors are unknown. Any patient who receives cemiplimab has a potential risk of developing ADAs.
Risk Minimisation Measures	Other routine risk minimisation measures beyond the Product Information: Legal status: Cemiplimab is subject to restricted medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

II.C Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

Not applicable.

II.C.2 Other Studies in Post-authorisation Development Plan

Not Applicable