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).

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.

(4) Cervical Cancer

LIBTAYO as a monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy

Further information about the evaluation of cemiplimab benefits can be found in cemiplimab EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage with the product's EPAR summary.

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:

- imARs
- IRRs

Important Potential Risks:

Lack of effect due to ADAs

Missing Information:

Long-term safety data

II.B Summary of Important Risks

Important Identified Risk: Immune-mediated Adverse Reactions	
Evidence for Linking the Risk to the Medicine	A total of 229 (20.5%) patients exposed to cemiplimab in clinical trials included in the RMP experienced at least 1 imAR. including 4 patients (0.4%) with grade 5, 7 patients (0.6%) with grade 4, 60 patients (5.4%) with grade 3 and imARs. Immune-mediated adverse reactions occurred in 20.5% of patients treated with cemiplimab in clinical trials including grade 5 (0.4%), Grade 4 (0.6%), grade 3 (5.4%), and grade 2 (10.9%). Fifty-one (4.6%) patients discontinued treatment due to imARs.
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 Guide and Alert Card

Important Identified Risk: Infusion-related Reactions	
Evidence for Linking the Risk to the Medicine	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 reaction occurred in 7.4% (83/1116) of patients receiving cemiplimab including 1 (<0.1%) patient with grade 3 IRRs. Infusion-related reaction led to

Important Identified Risk: Infusion-related Reactions	
	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.
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 Guide and Alert Card
Additional pharmacovigilance activities	Use of specific follow-up questionnaire for spontaneous post-authorisation reports of IRRs

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 5 clinical studies presented in this RMP (Study 1423, Study 1540, Study 1620, Study 1624 and Study 1676), the incidence of treatment-emergent ADA

Important Potential Risks: Lack of Effect due to Anti-drug Antibodies	
	was low (2.2%) in all patients receiving cemiplimab 350 mg Q3W. Antibody titers in all ADA-positive patients were all low. Of the patients who developed treatment-emergent antibodies to cemiplimab, none developed NAb. The incidence of persistent ADA was low (0.3%) in all patients receiving cemiplimab. Immunogenicity in patients with R/M cervical cancer from Study 1676 (206 patients, including 164 patients with SCC histology and 42 patients with AC histology), was low with no apparent difference in the occurrence of immunogenicity (ADA) based on histology. Pre-existing ADA occurred in 6 patients with R/M cervical cancer (2.9%). Treatment-emergent ADA (1.9% in total) was observed in 4 patients with SCC, 1 was transient and 3 were indeterminate; all were low titers (<1,000). None of the ADA-positive samples revealed the presence of neutralizing antibodies. No effect of immunogenicity/ADA on cemiplimab exposure was observed in patients with R/M cervical cancer in this study. The incidence of treatment-emergent ADA in patients with BCC in Study 1620 (3.2%) was similar to the incidence across all studies and cemiplimab dose regimens. The incidence of treatment-emergent ADA in patients with NSCLC in Study 1624 (2.3%) was consistent with the incidence observed across all studies. Only 1 patient (in Study 1423) showed evidence of altered PK profile with anti-cemiplimab antibody development; this was the only patient in the 4 studies with a moderate maximum titer. The presence of ADA was not associated with significant adverse events or imAEs.
Risk Factors and Risk Groups	Risk factors are unknown. Any patient who receives cemiplimab has a potential risk of developing ADAs.
Risk Minimisation Measures	Routine communication messages: SmPC sections 4.4 and 4.8 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

The following studies are conditions of the marketing authorisation:

Not applicable

Basal cell carcinoma

R2810-ONC-1620 (Group 1, mBCC) - A phase 2 study of cemiplimab in patients with advanced BCC who experienced progression of disease on Hedgehog Pathway Inhibitor therapy or were intolerant of prior Hedgehog Pathway Inhibitor therapy.

Rationale and Study Objectives:

To further confirm clinical efficacy and safety of cemiplimab in mBCC, the MAH should submit the primary analysis for mBCC and the final study report from clinical study 1620 evaluating objective response rate and duration of response of cemiplimab in patients with mBCC who experienced progression of disease on hedgehog pathway inhibitor therapy or were intolerant of prior hedgehog pathway inhibitor therapy.

The primary objective of the study was to estimate the ORR for mBCC (Group 1) or unresectable laBCC (Group 2), according to central review, when treated with cemiplimab monotherapy in patients who had progressed on HHI therapy, or were intolerant of prior HHI therapy.

Study Design:

This is an ongoing phase 2, non-randomized, 2-group, multicenter study of cemiplimab at a 350 mg dose administered IV Q3W in patients with advanced BCC who experienced progression of disease on HHI therapy, experienced a response no better than stable disease for at least 9 months or were intolerant of prior HHI therapy.

Study Population:

The study has 2 groups. Group 1 is for patients with metastatic BCC. Group 2 is for adult patients with locally advanced BCC.

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

Not applicable