Summary of the Risk Management Plan (RMP) for Libtayo®

Libtayo® (cemiplimab)

Marketing Autorisation Holder : sanofi-aventis (suisse) sa

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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 ”dénomination de la préparation” in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. sanofi-aventis (suisse) sa is fully responsible for the accuracy and correctness of the content of the published summary RMP of Libtayo.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for LIBTAYO (cemiplimab)

This is a summary of the risk management plan (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's risks and uncertainties (missing information).

Cemiplimab's 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's RMP.

I. The medicine and what it is used for

Cemiplimab is authorised for the treatment of adult patients with metastatic locally advanced (laCSCC) who are not candidates for curative surgery or curative radiation (see the Summary of Product Characteristics (SmPC) for the full indication). It contains cemiplimab as the active substance and it is given by intravenous (IV) infusion.

Further information about the evaluation of cemiplimab’s benefits can be found in cemiplimab’s European public assessment report (EPAR), including in its plain-language summary, available on the European Medicines Agency (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 periodic safety update report (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-related adverse reactions (irARs) **(**such as immune-related pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis, and other irARs)
- Infusion-related reactions

Important Potential Risks:

Lack of effect due to anti-drug antibodies

Missing Information:

Long-term safety data

II.B Summary of important risks

Important identified risk: Immune-related adverse reactions	
Evidence for linking the risk to the medicine	A total of 119 (20.1%) patients exposed to cemiplimab in clinical trials included in the RMP experienced at least 1 immune related adverse reaction including 4 patients (0.7%) with grade 5, 7 patients (1.2%) with grade 4, and 36 patients (6.1%) with grade 3 immune related adverse reactions. Twenty-six (4.4%) patients discontinued treatment due to immune related adverse reactions.

Important identified risk: Immune-related adverse reactions	
Risk factors and risk groups	Patients with a history of or ongoing autoimmune disease may be at higher risk of developing irAEs 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 related mucocutaneous adverse reactions.
Risk minimisation measures	Routine risk communication messages: SmPC section 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 and Study 1540, IRRs occurred in patients receiving cemiplimab. These have also been observed in patients exposed to other PD-1 inhibitors. Infusion-related reaction occurred in 9.1% (54/591) of patients receiving cemiplimab including 1 (0.2%) patient with grade 3 infusion-related reaction. Infusion-related reaction led to permanent discontinuation of cemiplimab in 2 (0.3%) patients. The most common symptoms of infusion-related reaction were nausea, pyrexia, vomiting, abdominal pain, chills, and flushing. All patients recovered from infusion-related reaction.

Important identified Risk: Infusion-related Reactions	
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 section 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
	Use of specific follow-up questionnaire for spontaneous post-authorisation reports of infusion-related reactions

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 2 clinical studies presented in this RMP, none of the patients with CSCC showed a positive response in the ADA assay. Therefore, NAbs were not assessed. As with all therapeutic proteins, there is a potential for immunogenicity with cemiplimab. Approximately 1.3% of 398 patients developed treatment emergent antibodies to cemiplimab. Of the patients who developed treatment emergent antibodies to cemiplimab, none developed NAbs. None of the patients with CSCC developed treatment emergent antibodies. Approximately 0.3% of all patients receiving cemiplimab 3 mg/kg Q2W had persistent antibody responses defined as having at least 2 consecutive positive post-baseline samples separated by at least 16 weeks. Antibody titers were low to moderate. In the few patients who developed anti-cemiplimab antibodies, there was no evidence of altered PK profile.
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 section 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:

R2810-ONC-1540 - A Phase 2 Study of REGN 2810, A Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6)

Rationale and Study Objectives

Group 6 will be conducted within Study 1540 for the purpose of confirming the efficacy and safety among patients with advanced CSCC treated with cemiplimab 350 mg Q3W IV and is intended to fulfill the regulatory requirements associated with conditional approval of cemiplimab. Group 6 is also designed to provide additional exploratory biomarker data.

The primary objective of this additional cohort is to confirm the clinical benefit of cemiplimab monotherapy for patients with advanced CSCC (metastatic or unresectable locally advanced) treated with cemiplimab 350 mg every 3 weeks (Q3W) IV.

Study Design

This is a phase 2, non-randomized, 6-group, multicenter pivotal trial evaluating the efficacy and safety of cemiplimab in patients with advanced CSCC. After a screening period of up to 28 days, patients in Group 6 will receive cemiplimab 350 mg Q3W IV on days 1, 22, and 43 (±3 days for each dose) during each 9-week treatment cycle. Patients will receive treatment until the 108-week treatment period is complete, or until disease progression, unacceptable toxicity or withdrawal of consent. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle; routine safety evaluations will be conducted at each cemiplimab dosing visit.

Screening is up to 4 weeks for all 6 groups. Patients in Group 6 will receive up to 108 weeks of treatment.

Study Population

Approximately 167 patients will be enrolled in Group 6. Group 6 will include elgible patients with metastatic (nodal and/or distant) CSCC and unresectable locally advanced CSCC.

R2810-ONC-1540 - A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Groups 1, 2 and 3)

The study included in the RMP, Study 1540, is ongoing and safety data from this study will be used to further characterise the long-term safety profile of cemiplimab and to further characterise identified risk of irARs. The study will provide additional safety data up to approximately 3.5 years of safety data for patients in Groups 1 and 2, and approximately 2.5 years of safety data for patients in Group 3.

II.C.2 Other studies in post-authorisation development plan

Not applicable