ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

LIBTAYO 350 mg concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate contains 50 mg of cemiplimab.

Each vial contains 350 mg of cemiplimab in 7 ml of solution.

Cemiplimab is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless to pale yellow solution with a pH of 6.0 and osmolality between 300 and 360 mmol/kg. The solution may contain trace amounts of translucent to white particles in a single-use vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LIBTAYO as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation.

4.2 Posology and method of administration

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

Posology

Recommended dose
The recommended dose is 350 mg cemiplimab, every 3 weeks, administered as an intravenous infusion over 30 minutes.

Treatment may be continued until disease progression or unacceptable toxicity.

Dose modifications
No dose reductions are recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Recommended modifications to manage adverse reactions are provided in Table 1.

Detailed guidelines for the management of immune-related adverse reactions are described in Table 1.

Table 1: Recommended treatment modifications			
Adverse reaction	**Severity[a]**	**Dose modification**	**Additional intervention**
Pneumonitis	Grade 2	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if pneumonitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue	Initial dose of 2 to 4 mg/kg/day prednisone or equivalent followed by a taper
Colitis	Grade 2 or 3	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if colitis or diarrhoea improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 4 or recurrent Grade 3	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Hepatitis	Grade 2 with AST or ALT >3 and ≤5×ULN or total bilirubin >1.5 and ≤3×ULN	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if hepatitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper	
	Grade ≥3 with AST or ALT >5×ULN or total bilirubin >3×ULN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Hypothyroidism	Grade 3 or 4	Withhold LIBTAYO	Initiate thyroid hormone replacement as clinically indicated
		Resume LIBTAYO when hypothyroidism returns to Grade 0 to 1 or is otherwise clinically stable	
Hyperthyroidism	Grade 3 or 4	Withhold LIBTAYO	Initiate symptomatic management
		Resume LIBTAYO when hyperthyroidism returns to Grade 0 to 1 or is otherwise clinically stable	
Hypophysitis	Grade 2 to 4	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated

Table 1: Recommended treatment modifications			
Adverse reaction	**Severity[a]**	**Dose modification**	**Additional intervention**
		Resume LIBTAYO if hypophysitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or is otherwise clinically stable	
Adrenal insufficiency	Grade 2 to 4	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if adrenal insufficiency improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or is otherwise clinically stable	
Type 1 diabetes mellitus	Grade 3 or 4 (hyperglycaemia)	Withhold LIBTAYO	Initiate treatment with anti-hyperglycaemics as clinically indicated
		Resume LIBTAYO when diabetes mellitus returns to Grade 0 to 1 or is otherwise clinically stable	
Skin adverse reactions	Grade 2 lasting longer than 1 week, Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if skin reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 4 or confirmed SJS or TEN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-related skin reaction or other immune-related adverse reactions in patients with prior treatment with idelalisib	Grade 2	Withhold LIBTAYO	Initiate symptomatic management immediately, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if skin reaction or other immune-related adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 3 or 4 (excluding endocrinopathies) or recurrent Grade 2	Permanently discontinue	Initiate symptomatic management immediately, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Nephritis	Grade 2	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper

Table 1: Recommended treatment modifications			
Adverse reaction	**Severity[a]**	**Dose modification**	**Additional intervention**
		Resume LIBTAYO if nephritis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 3 or 4	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Other immune-related adverse reactions (including but not limited to meningitis, paraneoplastic encephalomyelitis, arthritis, Guillain-Barre syndrome, encephalitis, chronic inflammatory demyelinating polyradiculoneuropathy, central nervous system inflammation, autoimmune myocarditis, and immune thrombocytopenic purpura, myalgia, Sjogren's syndrome, vasculitis, myasthenia gravis)[b]	Grade 3 clinical signs or symptoms of an immune-related adverse reaction not described above	Withhold LIBTAYO	Initiate symptomatic management
		Resume LIBTAYO if other immune-related adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	– Grade 4 adverse reaction (excluding endocrinopathies) – Recurrent severe Grade 3 immune-related adverse reaction – Persistent Grade 2 or 3 immune-related adverse reactions lasting 12 weeks or longer (excluding endocrinopathies) – Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Infusion-related reaction	Grade 1 or 2	Interrupt or slow rate of infusion	Initiate symptomatic management
	Grade 3 or 4	Permanently discontinue	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

[a] Toxicity should be graded with the current version of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

[b] Observed with LIBTAYO or with other anti-PD-1/PD-L1 monoclonal antibodies

Patient Alert Card

All prescribers of LIBTAYO should be familiar with the educational materials and inform the patients about the Patient Alert Card explaining what to do should they experience any symptom of immune-related adverse reactions and infusion-related reactions. The physician will provide the Patient Alert Card to each patient.

Special populations

Paediatric population
The safety and efficacy of LIBTAYO in children and adolescents below the age of 18 years have not been established. No data are available.

Elderly
No dose adjustment is recommended for elderly patients. Cemiplimab exposure is similar across all age groups (see sections 5.1 and 5.2).

Renal impairment
No dose adjustment of LIBTAYO is recommended for patients with renal impairment. There are limited data for LIBTAYO in patients with severe renal impairment CLcr <30 ml/min (see section 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild hepatic impairment. LIBTAYO has not been studied in patients with moderate or severe hepatic impairment. There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations (see section 5.2).

Method of administration

LIBTAYO is for intravenous use. It must be administered by intravenous infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding, in-line or add-on filter (0.2 micron to 5 micron pore size).

Other medicinal products should not be co-administered through the same infusion line.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Immune-related adverse reactions
Severe and fatal immune-related adverse reactions have been observed with cemiplimab (see section 4.8). These immune-related reactions may involve any organ system. Most immune-related reactions initially manifest during treatment with cemiplimab; however, immune-related adverse reactions can occur after discontinuation of cemiplimab.

Immune-related adverse reactions should be managed with cemiplimab treatment modifications, hormone replacement therapy (if clinically indicated), and corticosteroids. For suspected immune-related adverse reactions, patients should be evaluated to confirm an immune-related adverse reaction and to exclude other possible causes. Depending upon the severity of the adverse reaction, cemiplimab should be withheld or permanently discontinued (see section 4.2).

Immune-related pneumonitis
Immune-related pneumonitis, defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases, has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis. Patients with suspected

pneumonitis should be evaluated with radiographic imaging as indicated based on clinical evaluation and managed with cemiplimab treatment modifications and corticosteroids. (see section 4.2).

Immune-related colitis
Immune-related diarrhoea or colitis, defined as requiring use of corticosteroids with no clear alternate aetiology, has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for signs and symptoms of diarrhoea or colitis and managed with cemiplimab treatment modifications, anti-diarrhoeal agents, and corticosteroids (see section 4.2).

Immune-related hepatitis
Immune-related hepatitis, defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases, has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for abnormal liver tests prior to and periodically during treatment as indicated based on clinical evaluation and managed with cemiplimab treatment modifications and corticosteroids (see section 4.2).

Immune-related endocrinopathies
Immune-related endocrinopathies, defined as treatment-emergent endocrinopathies with no clear alternate aetiology, have been observed in patients receiving cemiplimab (see section 4.8).

Thyroid disorders (Hypothyroidism/Hyperthyroidism)
Immune-related thyroid disorders have been observed in patients receiving cemiplimab. Thyroid disorders can occur at any time during the treatment. Patients should be monitored for changes in thyroid function at the start of treatment and periodically during the treatment as indicated based on clinical evaluation (see section 4.8). Patients should be managed with hormone replacement therapy (if indicated) and cemiplimab treatment modifications. Hyperthyroidism should be managed according to standard medical practice (see section 4.2).

Hypophysitis
Immune-related hypophysitis has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for signs and symptoms of hypophysitis and managed with cemiplimab treatment modifications and corticosteroids (see section 4.2).

Adrenal insufficiency
Adrenal insufficiency has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for signs and symptoms of adrenal insufficiency during and after treatment and managed with cemiplimab treatment modifications and corticosteroids (see section 4.2).

Type 1 Diabetes mellitus
Immune-related type 1 diabetes mellitus, including diabetic ketoacidosis, has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for hyperglycaemia and signs and symptoms of diabetes as indicated based on clinical evaluation and managed with oral anti-hyperglycaemics or insulin and cemiplimab treatment modifications (see section 4.2). Cemiplimab should be withheld and anti-hyperglycaemics or insulin should be administered in patients with severe or life-threatening (Grade ≥ 3) hyperglycaemia. Cemiplimab should be resumed when metabolic control is achieved on insulin replacement or anti-hyperglycaemics (see section 4.2).

Immune-related skin adverse reactions
Immune-related skin adverse reactions, defined as requiring use of systemic corticosteroids with no clear alternate aetiology, including severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (some cases with fatal outcome), and other skin reactions such as rash, erythema multiforme, pemphigoid, have been reported in association with cemiplimab treatment (see section 4.8).

Patients should be monitored for evidence of suspected severe skin reactions and exclude other causes. Patients should be managed with cemiplimab treatment modifications and corticosteroids (see section 4.2).

Cases of SJS, fatal TEN and stomatitis occurred following 1 dose of cemiplimab in patients with prior exposure to idelalisib, who were participating in a clinical trial evaluating cemiplimab in Non-Hodgkin Lymphoma (NHL), and who had recent exposure to sulfa containing antibiotics (see section 4.8). Patients should be managed with cemiplimab treatment modifications and corticosteroids as described above (see section 4.2).

Immune-related nephritis
Immune-related nephritis, defined as requiring use of corticosteroids with no clear alternate aetiology, has been observed in patients receiving cemiplimab (see section 4.8). Patients should be managed with cemiplimab treatment modifications and corticosteroids (see section 4.2).

Other immune-related adverse reactions
Other fatal and life-threatening immune-related adverse reactions have been observed in patients receiving cemiplimab including paraneoplastic encephalomyelitis and meningitis (see section 4.8 for other immune-related adverse reactions).

Patients should be monitored for signs and symptoms of immune-related adverse reactions and managed with cemiplimab treatment modifications and corticosteroids (see section 4.2).

Infusion-related reactions
Cemiplimab can cause severe or life-threatening infusion-related reactions (see section 4.8). Patients should be monitored for signs and symptoms of infusion-related reactions and managed with cemiplimab treatment modifications and corticosteroids. Cemiplimab should be interrupted or the rate of infusion slowed for mild or moderate infusion-related reactions. The infusion should be stopped and cemiplimab should be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions (see section 4.2).

Patients excluded from clinical studies
Patients that had active infections or that were immunocompromised were not included in the main study. For a full list of patients excluded from clinical trials, see section 5.1.

In the absence of data, cemiplimab should be used with caution in these populations after careful evaluation of the balance of benefits and risks for the patient.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic drug-drug interaction studies have been conducted with cemiplimab.

The use of systemic corticosteroids or immunosuppressants before starting cemiplimab, except for physiological doses of systemic corticosteroid (≤10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of cemiplimab. However, systemic corticosteroids or other immunosuppressants can be used after starting cemiplimab to treat immune-related adverse reactions (see sections 4.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective contraception during treatment with cemiplimab and for at least 4 months after the last dose of cemiplimab.

Pregnancy
Animal reproduction studies have not been conducted with cemiplimab. There are no available data on the use of cemiplimab 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 foetus resulting in foetal death (see section 5.3).

Human IgG4 is known to cross the placental barrier and cemiplimab is an IgG4; therefore, cemiplimab has the potential to be transmitted from the mother to the developing foetus. Cemiplimab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk.

Breast-feeding
It is unknown whether cemiplimab is secreted in human milk. It is known that antibodies (including IgG4) are secreted in human milk; a risk to the breast-feeding newborns/infants cannot be excluded.

If a woman chooses to be treated with cemiplimab, she should be instructed not to breast-feed while being treated with cemiplimab and for at least 4 months after the last dose.

Fertility
No clinical data are available on the possible effects of cemiplimab on fertility. No effects on fertility assessment parameters or in the male and female reproductive organs were observed in a 3-month repeat dose fertility assessment study with sexually mature cynomolgus monkeys.

4.7 Effects on ability to drive and use machines

Cemiplimab has no or negligible influence on the ability to drive and use machines. Fatigue has been reported following treatment with cemiplimab (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
Immune-related adverse reactions can occur with cemiplimab. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of cemiplimab (see "Description of selected adverse reactions" below).

The safety of cemiplimab has been evaluated in 591 patients with advanced solid malignancies including 219 advanced CSCC patients who received cemiplimab monotherapy in 2 clinical studies (R2810-ONC-1423 and R2810-ONC-1540). Immune-related adverse reactions occurred in 20.1% of patients treated with cemiplimab in clinical trials including Grade 5 (0.7%), Grade 4 (1.2%) and Grade 3 (6.1%). Immune-related adverse reactions led to permanent discontinuation of cemiplimab in 4.4% of patients. The most common immune-related adverse reactions were hypothyroidism (7.1%), pneumonitis (3.7%), immune-related skin adverse reactions (2.0%), hyperthyroidism (1.9%) and hepatitis (1.9%) (see "Description of selected adverse reactions" below, Special warnings and precautions for use in section 4.4 and Recommended treatment modifications in section 4.2). Adverse reactions were serious in 8.6% patients and led to permanent discontinuation of cemiplimab in 5.8% of patients.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with cemiplimab treatment (see section 4.4).

Tabulated list of adverse reactions
Listed in Table 2 are adverse reactions by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Tabulated list of adverse reactions in patients treated with cemiplimab			
System organ class preferred term	**Grades 1-5 (Frequency category)**	**Grades 1-5 (%)**	**Grades 3-5 (%)**
Immune system disorders			
Infusion-related reaction	Common	4.1	0
Sjogren's syndrome	Uncommon	0.5	0
Immune thrombocytopenic purpura	Uncommon	0.2	0
Vasculitis	Uncommon	0.2	0
Endocrine disorders			
Hypothyroidism	Common	9.6	0
Hyperthyroidism	Common	2.7	0
Type 1 diabetes mellitus[a]	Uncommon	0.7	0.7
Adrenal insufficiency	Uncommon	0.5	0.5
Hypophysitis	Uncommon	0.5	0.5
Thyroiditis	Uncommon	0.2	0
Nervous system disorders			
Paraneoplastic encephalomyelitis	Uncommon	0.2	0.2
Chronic inflammatory demyelinating polyradiculoneuropathy	Uncommon	0.5	0
Encephalitis	Uncommon	0.5	0.5
Meningitis[b]	Uncommon	0.5	0.5
Guillain-Barre syndrome	Uncommon	0.2	0.2
Central nervous system inflammation	Uncommon	0.2	0
Neuropathy peripheral[c]	Uncommon	0.5	0
Myasthenia gravis	Uncommon	0.2	0
Eye disorders			
Keratitis	Uncommon	0.5	0
Cardiac disorders			
Myocarditis[d]	Uncommon	0.5	0.5
Pericarditis	Uncommon	0.5	0.5
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	Common	5.9	2.3
Gastrointestinal disorders			
Diarrhoea[e]	Very common	13.2	0.5
Stomatitis	Common	2.4	0
Hepatobiliary disorders			
Hepatitis[f]	Common	1.4	1.4
Skin and subcutaneous skin disorders			
Rash[g]	Very common	23.3	1.4

Table 2: Tabulated list of adverse reactions in patients treated with cemiplimab			
System organ class preferred term	**Grades 1-5 (Frequency category)**	**Grades 1-5 (%)**	**Grades 3-5 (%)**
Pruritus[h]	Very common	12.3	0
Musculoskeletal and connective tissue disorders			
Arthralgia	Common	5.0	0
Musculoskeletal pain[i]	Common	4.1	0.5
Arthritis[j]	Common	1.4	0.5
Muscular weakness	Uncommon	0.9	0
Renal and urinary disorders			
Nephritis	Uncommon	0.5	0
General disorders and administration site conditions			
Fatigue[k]	Very common	21.5	0.9
Investigations			
Alanine aminotransferase increased	Common	5.5	0.5
Aspartate aminotransferase increased	Common	5.0	0.9
Blood alkaline phosphatase increased	Common	2.7	0
Blood creatinine increased	Common	1.8	0

Version v.4.03 of NCI CTCAE was used to grade toxicity.

a. Type 1 diabetes mellitus is a composite term that includes diabetes mellitus, diabetic ketoacidosis and type 1 diabetes mellitus.
b. Meningitis is a composite term that includes meningitis and meningitis aseptic.
c. Neuropathy peripheral is a composite term that includes neuropathy peripheral and neuritis.
d. Myocarditis is a composite term that includes autoimmune myocarditis and myocarditis.
e. Diarrhoea is a composite term that includes diarrhoea and colitis.
f. Hepatitis is a composite term that includes hepatitis and autoimmune hepatitis.
g. Rash is a composite term that includes rash maculo-papular, rash, dermatitis, rash generalised, dermatitis bullous, drug eruption, erythema, pemphigoid, psoriasis, rash erythematous, rash macular, rash pruritic and skin reaction.
h. Pruritus is a composite term that includes pruritus and pruritus allergic.
i. Musculoskeletal pain is a composite term that includes back pain, musculoskeletal pain, myalgia, neck pain and pain in extremity.
j. Arthritis is a composite term that includes arthritis and polyarthritis.
k. Fatigue is a composite term that includes fatigue and asthenia.

Description of selected adverse reactions

The selected adverse reactions described below are based on safety of cemiplimab in 591 patients in uncontrolled clinical studies.

Immune-related adverse reactions (see section 4.4)

Immune-related pneumonitis

Immune-related pneumonitis occurred in 22 (3.7%) of 591 patients receiving cemiplimab, including 2 (0.3%) patients with Grade 5, 2 (0.3%) patients with Grade 4, and 6 (1.0%) patients with Grade 3 pneumonitis. Immune-related pneumonitis led to permanent discontinuation of cemiplimab in 11 (1.9%) of 591 patients. Among the 22 patients with immune-related pneumonitis, the median time to onset was 3.8 months (range: 7 days to 18 months) and the median duration of pneumonitis was 21.5 days (range: 5 days to 6.5 months). Eighteen patients (3.0%) received high-dose corticosteroids for a median of 8.5 days (range: 1 day to 5.9 months). Resolution of pneumonitis had occurred in 14 (63.6%) of the 22 patients at the time of data cut-off.

Immune-related colitis
Immune-related diarrhoea or colitis occurred in 7 (1.2%) of 591 patients receiving cemiplimab including 2 (0.3%) with Grade 3 immune-related diarrhoea or colitis. Immune-related diarrhoea or colitis led to permanent discontinuation of cemiplimab in 1 (0.2%) of 591 patients. Among the 7 patients with immune-related diarrhoea or colitis, the median time to onset was 3.8 months (range: 15 days to 6.0 months) and the median duration of immune-related diarrhoea or colitis was 30 days (range: 4 days to 8.6 months). Four patients (0.7%) with immune-related diarrhoea or colitis received high-dose corticosteroids for a median of 29 days (range: 19 days to 2.0 months). Resolution of immune-related diarrhoea or colitis had occurred in 4 (57.1%) of the 7 patients at the time of data cut-off.

Immune-related hepatitis
Immune-related hepatitis occurred in 11 (1.9%) of 591 patients receiving cemiplimab including 1 (0.2%) patient with Grade 5, 1 (0.2%) patient with Grade 4, and 9 (1.5%) patients with Grade 3 immune-related hepatitis. Immune-related hepatitis led to permanent discontinuation of cemiplimab in 5 (0.8%) of 591 patients. Among the 11 patients with immune-related hepatitis, the median time to onset was 1.0 month (range: 7 days to 4.2 months) and the median duration of hepatitis was 15 days (range: 8 days to 2.7 months). Ten (1.7%) patients with immune-related hepatitis received high-dose corticosteroids for a median of 10.5 days (range: 2 days to 1.9 months). Resolution of hepatitis had occurred in 8 (72.7%) of the 11 patients at the time of data cut-off.

Immune-related endocrinopathies

Hypothyroidism occurred in 42 (7.1%) of 591 patients receiving cemiplimab including 1 (0.2%) patient with Grade 3 hypothyroidism. No patient discontinued cemiplimab due to hypothyroidism. Among the 42 patients with hypothyroidism, the median time to onset was 4.2 months (range: 15 days to 18.9 months).

Hyperthyroidism occurred in 11 (1.9%) of 591 patients receiving cemiplimab including 1 (0.2%) patient with Grade 3 hyperthyroidism. No patient discontinued cemiplimab due to hyperthyroidism. Among the 11 patients with hyperthyroidism, the median time to onset was 1.9 months (range: 28 days to 14.8 months).

Adrenal insufficiency occurred in 3 (0.5%) of 591 patients receiving cemiplimab including 1 (0.2%) patient with Grade 3 adrenal insufficiency. No patient discontinued cemiplimab due to adrenal insufficiency. Among the 3 patients with adrenal insufficiency, the median time to onset was 11.5 months (range: 10.4 months to 12.3 months). One of the 3 patients was treated with systemic corticosteroids.

Immune-related hypophysitis occurred in 1 (0.2%) of 591 patients receiving cemiplimab. The event was Grade 3 hypophysitis.

Type 1 diabetes mellitus without an alternative aetiology occurred in 4 (0.7%) of 591 patients including 3 (0.5%) patients with Grade 4 and 1 (0.2%) patient with Grade 3 type 1 diabetes mellitus. Type 1 diabetes mellitus led to permanent discontinuation of cemiplimab in 1 (0.2%) of 591 patients. Among the 4 patients with type 1 diabetes mellitus, the median time to onset was 2.3 months (range: 28 days to 6.2 months).

Immune-related skin adverse reactions
Immune-related skin adverse reactions occurred in 12 (2.0%) of 591 patients receiving cemiplimab including 6 (1.0%) patients with Grade 3 immune-related skin adverse reactions. Immune-related skin adverse reactions led to permanent discontinuation of cemiplimab in 2 (0.3%) of 591 patients. Among the 12 patients with immune-related skin adverse reactions, the median time to onset was 1.5 months (range: 2 days to 10.9 months) and the median duration was 4.4 months (range: 14 days to 9.6 months). Nine patients (1.5%) with immune-related skin adverse reactions received high-dose corticosteroids for a median of 16 days (range: 7 days to 2.6 months). Resolution had occurred in 6 (50%) of 12 patients at the time of data cut-off.

Immune-related nephritis
Immune-related nephritis occurred in 3 (0.5%) of 591 patients receiving cemiplimab including 2 (0.3%) patients with Grade 3 immune-related nephritis. Immune-related nephritis led to permanent discontinuation of cemiplimab in 1 (0.2%) of 591 patients. Among the 3 patients with immune-related nephritis, the median time to onset was 1.8 months (range: 29 days to 4.1 months) and the median duration of nephritis was 18 days (range: 9 days to 29 days). Two (0.3%) patients with immune-related nephritis received high-dose corticosteroids for a median of 1.5 months (range: 16 days to 2.6 months). Resolution of nephritis had occurred in all patients at the time of data cut-off.

Other immune-related adverse reactions
The following clinically significant, immune-related adverse reactions occurred at an incidence of less than 1% of 591 patients treated with cemiplimab. The events were Grade 3 or less unless stated otherwise:

Nervous system disorders: Meningitis[a] (Grade 4), Paraneoplastic encephalomyelitis (Grade 5), Guillain-Barre syndrome, central nervous system inflammation, Chronic inflammatory demyelinating polyradiculoneuropathy, Encephalitis[b], Myasthenia gravis, Neuropathy peripheral.
Cardiac Disorders: Myocarditis[c], Pericarditis
Immune system disorders: Immune thrombocytopenic purpura
Vascular disorders: Vasculitis
Musculoskeletal and connective tissue disorders: Myalgia, Arthritis[d], Sjogren's syndrome
Eye disorders: Keratitis
Gastrointestinal disorders: Stomatitis
[a] includes meningitis and meningitis aseptic
[b] includes encephalitis and noninfective encephalitis
[c] includes autoimmune myocarditis and myocarditis
[d] includes arthritis and polyarthritis

Infusion-related reactions
Infusion-related reactions occurred in 54 (9.1%) of 591 patients treated with 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 the infusion-related reaction.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity with cemiplimab. Five out of 398 patients (1.3%) administered cemiplimab developed treatment-emergent antibodies, with 1 out of 398 patients (0.3%) exhibiting persistent antibody responses. No neutralizing antibodies have been observed. There was no evidence of an altered pharmacokinetic or safety profile with anti-cemiplimab antibody development.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: not yet assigned

Mechanism of action

Cemiplimab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with its ligands PD-L1 and PD-L2. Engagement of PD-1 with its ligands PD-L1 and PD-L2, which are expressed by antigen presenting cells and may be expressed by tumour cells and/or other cells in the tumour microenvironment, results in inhibition of T cell function such as proliferation, cytokine secretion, and cytotoxic activity. Cemiplimab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Clinical efficacy and safety

The efficacy and safety of cemiplimab in patients with metastatic (nodal or distant) CSCC (mCSCC) or locally advanced CSCC (laCSCC) who were not candidates for curative surgery or curative radiation were studied in clinical trial R2810-ONC-1540 (Study 1540). Study 1540 was a phase 2, open-label, multi-centre study that had enrolled 193 patients with mCSCC or laCSCC with a combined median follow-up time of 9.4 months total. Median follow-up was 16.5 months for the mCSCC 3 mg/kg every 2 weeks group, 9.3 months for the laCSCC 3 mg/kg every 2 weeks group and 8.1 months for the mCSCC 350 mg every 3 weeks group.

Patients with any of the following were excluded: autoimmune disease that required systemic therapy with immunosuppressant agents within 5 years; history of solid organ transplant; history of pneumonitis within the last 5 years; prior treatment with anti-PD-1/PD-L1 or other immune checkpoint inhibitor therapy; active infection requiring therapy, including known infection with human immunodeficiency virus, or active infection with hepatitis B or hepatitis C virus; chronic lymphocytic leukaemia (CLL); brain metastases or Eastern Cooperative Oncology Group (ECOG) performance score ≥ 2.

In Study 1540, patients received cemiplimab until progression of disease, unacceptable toxicity or completion of planned treatment [3 mg/kg every 2 weeks for 96 weeks or 350 mg every 3 weeks for 54 weeks]. If patients with locally advanced disease showed sufficient response to treatment, surgery with curative intent was permitted. Tumour response assessments were performed every 8 or 9 weeks (for patients receiving 3 mg/kg every 2 weeks or 350 mg every 3 weeks, respectively). The primary endpoint of Study 1540 was confirmed objective response rate (ORR), as assessed by independent central review (ICR). For patients with metastatic CSCC without externally visible target lesions, ORR was determined by Response Evaluation Criteria in Solid Tumours (RECIST 1.1). For patients with externally visible target lesions (locally advanced CSCC and metastatic CSCC), ORR was determined by a composite endpoint that integrated ICR assessments of radiologic data (RECIST 1.1) and digital medical photography (WHO criteria). Secondary endpoints were duration of response (DOR) by ICR and by investigator assessment (IA), ORR by IA, progression free survival (PFS) by ICR and IA, overall survival (OS), complete response rate (CRR) by ICR, and change in scores in patient reported outcomes on the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30).

Results are presented from 193 patients in Study 1540. Of these 193 patients, 115 had mCSCC and 78 had laCSCC. The median age was 72 years (range: 38 to 96): Seventy-eight (40.4%) patients were 75 years or older, 66 patients (34.2%) were 65 to less than 75 years, and 49 patients (25.4%) were less than 65 years. A total of 161 (83.4 %) patients were male, and 187 (96.9%) patients were White; the ECOG performance score was 0 (44.6%) or 1 (55.4%). Thirty-three and 7/10 per cent (33.7%) of patients had received at least 1 prior anti-cancer systemic therapy, 90.2% of patients had received prior

cancer related surgery, and 67.9% of patients had received prior radiotherapy. Among patients with mCSCC, 76.5% had distant metastases, and 22.6% had only nodal metastases.

Efficacy results for Study 1540 are presented in Table 3.

Table 3: Efficacy results – Study 1540 – metastatic CSCC by dosing group, locally advanced CSCC

	mCSCC cemiplimab: 3 mg/kg Q2W (Group 1) (N = 59) ICR	laCSCC cemiplimab: 3 mg/kg Q2W (Group 2) (N = 78) ICR	mCSCC cemiplimab: 350 mg Q3W (Group 3) (N = 56) ICR
Confirmed objective response rate (ORR)[a]			
ORR	49.2%	43.6%	39.3%
95% CI for ORR	(35.9, 62.5)	(32.4, 55.3)	(26.5, 53.2)
Complete response (CR)[b]	16.9%	12.8%	3.6%
Partial response (PR)	32.2%	30.8%	35.7%
Stable disease (SD)	15.3%	35.9%	14.3%
Progressive disease (PD)	16.9%	11.5%	26.8%
Duration of response (DOR)[a]			
Median (range) (months)	NR (2.8-21.6+)	NR (1.9 – 24.2+)	NR (2.1-11.1+)
Patients with DOR ≥ 6 months, %	93.1%	67.6%	63.6%
Time to response			
Median (months) range (min:max)	1.9 (1.7: 9.1)	1.9 (1.8: 8.8)	2.1 (2.0: 8.3)
Progression free survival (PFS)[a, c]			
6 months	66.0% (52.0, 76.8)	71.5% (58.9, 80.9)	59.3% (45.0, 71.0)
12 months	53.1% (39.1, 65.2)	58.1% (43.7, 70.0)	44.6% (26.5, 61.3)
Overall survival[a, c, d]			
12 months	81.3% (68.7, 89.2)	93.2% (84.4, 97.1)	76.1% (56.9, 87.6)

Data cut-off was Sep 20, 2018 for Groups 1 and 3 patients, and Oct 10, 2018 for Group 2 patients.
CI: confidence interval; ICR: Independent Central Review; NR: Not Reached; +: Denotes ongoing at last assessment

a. In Groups 1, 2, and 3, median durations of follow-up were 16.5, 9.3, and 8.1 months, respectively.
b. Only includes patients with complete healing of prior cutaneous involvement; locally advanced CSCC patients in Study 1540 required biopsy to confirm complete response.
c. Based on Kaplan Meier estimates
d. Overall survival does not require central review.

Efficacy and PD-L1 status

Clinical activity was observed regardless of tumour PD-L1 expression status. The relationship between PD-L1 status and efficacy was analysed post-hoc in patients with available tissue samples. Overall in Studies 1423 and 1540, PD-L1 IHC results were available for 75 advanced CSCC patients. Among

22 advanced CSCC patients with PD-L1 < 1%, ORR per independent central review was 40.9% (9/22). Among 53 advanced CSCC patients with PD-L1 ≥ 1%, ORR was 54.7% (29/53). Among 21 mCSCC patients, ORR was 60% (3/5) in patients with PD-L1 < 1% and 56.3% (9/16) among patients with PD-L1 ≥ 1%. Among 54 patients with laCSCC, ORR was 35.3% (6/17) in patients with PD-L1 < 1% and 54.1% (20/37) among patients with PD-L1 ≥ 1%.

Elderly population
Of the 219 patients with mCSCC and laCSCC treated with cemiplimab, 25.1% (55/219) were less than 65 years, 34.2% (75/219) were 65 to less than 75 years, and 40.6% (89/219) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

In the 193 patients in the efficacy analysis, the objective response rate by ICR (95% CI) was 40.8% (27.0%, 55.8%) in patients less than 65 years, 48.5% (36.0%, 61.1%) in patients 65 to less than 75 years, and 42.3% (31.2%, 54.0%) in patients 75 years or older.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with cemiplimab in all subsets of the paediatric population in the treatment of all conditions included in the category of malignant neoplasms, except haematopoietic and lymphoid tissue (see section 4.2 for information on paediatric use).

Conditional approval
This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Concentration data were collected in 548 patients with various solid tumours, including 178 patients with CSCC, who received cemiplimab. At dosing regimens of 1 mg/kg to 10 mg/kg every 2 weeks and 350 mg every 3 weeks, kinetics of cemiplimab were observed to be linear and dose proportional, suggesting saturation of the target-mediated pathway over the dosing interval. Similar exposures to cemiplimab are achieved with the doses of 350 mg every 3 weeks and 3 mg/kg every 2 weeks. With 350 mg every 3 weeks, the mean steady-state concentration of cemiplimab ranged between C_{max} of 168 mg/l and a C_{trough} of 61 mg/l. Steady-state exposure is achieved after approximately 4 months of treatment.

Absorption
Cemiplimab is administered via the intravenous route and hence is completely bioavailable.

Distribution
Cemiplimab is primarily distributed in the vascular system with a volume of distribution at steady-state (V_{ss}) is 5.2 l.

Biotransformation
Specific metabolism studies were not conducted because cemiplimab is a protein. Cemiplimab is expected to degrade to small peptides and individual amino acids.

Elimination
Clearance of cemiplimab is linear at doses of 1 mg/kg to 10 mg/kg every two weeks. Cemiplimab clearance after the first dose is approximately 0.33 l/day. The total clearance appears to decrease by approximately 35% over time, resulting in a steady state clearance (CLss) of 0.21 l/day; the decrease in CL is not considered clinically relevant. The within dosing interval half-life at steady state is 19.4 days.

Linearity/non-linearity
At the dosing regimens of 1 mg/kg to 10 mg/kg every two weeks, kinetics of cemiplimab were observed to be linear and dose proportional, suggesting saturation of the target-mediated pathway.

Special populations
A population PK analysis suggests that the following factors have no clinically significant effect on the exposure of cemiplimab: age, gender, body weight, race, cancer type, albumin level, mild hepatic impairment and renal impairment.

Renal impairment
The effect of renal impairment on the exposure of cemiplimab was evaluated by a population PK analysis in patients with mild (CLcr 60 to < 89 ml/min; n= 197), moderate (CLcr 30 to < 60 ml/min; n= 90), or severe (CLcr <30 ml/min; n= 4) renal impairment. No clinically important differences in the exposure of cemiplimab were found between patients with renal impairment and patients with normal renal function. Cemiplimab has not been studied in patients with CLcr <25 ml/min (see section 4.2).

Hepatic impairment
The effect of hepatic impairment on the exposure of cemiplimab was evaluated by population PK analysis. In patients with mild hepatic impairment (n= 5) (total bilirubin [TB] greater than 1.0 to 1.5 times the upper limit of normal [ULN] and any aspartate aminotransferase [AST]); no clinically important differences in the exposure of cemiplimab were found compared to patients with normal hepatic function. Cemiplimab has not been studied in patients with moderate or severe hepatic impairment. There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations (see section 4.2).

5.3 Preclinical safety data

No studies have been performed to test the potential of cemiplimab for carcinogenicity or genotoxicity. Animal reproduction studies have not been conducted with cemiplimab (see section 4.6). As reported in the literature, PD-1 / PD-L1 signalling pathway plays a role in sustaining pregnancy by maintaining immunological tolerance and studies have shown that PD-1 receptor blockade results in early termination of pregnancy. The increase of spontaneous abortion and/or resorption in animals with restricted PD-L1 expression (knock-out or anti-PD1 / PD-L1 monoclonal antibodies) has been shown in both mice and monkeys. These animal species have similar maternal-foetal interface to that in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine monohydrochloride monohydrate
Sucrose
L-proline
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
30 months

After opening
Once opened, the medicinal product should be diluted and infused immediately.

After preparation of infusion
Once prepared, administer the diluted solution immediately. If diluted solution is not administered immediately, it may be stored temporarily either:

- at room temperature up to 25°C for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion solution in the intravenous container and time for administration of the infusion.
  Or
- under refrigeration at 2°C to 8°C for no more than 24 hours from the time of infusion preparation. Do not freeze. Allow the diluted solution to come to room temperature prior to administration.

6.4 Special precautions for storage

Unopened vial
Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original carton in order to protect from light.

For storage conditions after first opening or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

LIBTAYO is provided in a 10 ml clear Type 1 glass vial, with a grey chlorobutyl stopper with FluroTec coating and seal cap with a flip-off button.

Each carton contains 1 vial.

6.6 Special precautions for disposal and other handling

Preparation and administration

- Visually inspect medicinal product for particulate matter and discoloration prior to administration. LIBTAYO is a clear to slightly opalescent, colourless to pale yellow solution that may contain trace amounts of translucent to white particles
- Discard the vial if the solution is cloudy, discoloured or contains extraneous particulate matter other than a few translucent-to-white particles.
- Do not shake the vial.
- Withdraw 7 ml (350 mg) from the vial of LIBTAYO and transfer into an intravenous infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection. Mix the diluted solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should be between 1 mg/ml to 20 mg/ml.
- LIBTAYO must be administered by intravenous infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding, in-line or add-on filter (0.2 micron to 5 micron pore size).
- Do not co-administer other medicinal products through the same infusion line.

LIBTAYO is for single use only. Dispose of any unused medicinal product or waste material in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Regeneron Ireland Designated Activity Company (DAC)
Europa House
Harcourt Centre
Harcourt Street
Dublin 2
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1376/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike
Rensselaer, NY 12144
United States

Name and address of the manufacturer(s) responsible for batch release

Regeneron Ireland DAC
Raheen Business Park
Limerick
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of LIBTAYO in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and

any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where LIBTAYO is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use LIBTAYO have access to/are provided with the following educational package:
- A patient guide
- A patient alert card

- **The patient guide** shall contain the following key messages
    - Description of the main signs or symptoms of the immune-related adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other irARs) and infusion related reactions, and the importance of notifying their treating physician immediately if symptoms occur.
    - The importance of not attempting to self-treat any symptoms without consulting their healthcare professional first.
    - The importance of carrying the Patient Alert Card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals).
    - A reminder that all known or suspected adverse drug reactions (ADRs) can also be reported to local regulatory authorities.

- **The patient alert card** shall contain the following key messages:
    - A warning message for health care professionals treating the patient at any time, including in conditions of emergency, that the patient is treated with LIBTAYO.
    - Description of the main signs or symptoms of the immune-related adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other irARs) and infusion related reactions, and the importance of notifying their treating physician immediately if symptoms occur.
    - The contact details of their LIBTAYO prescriber.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation, the MAH should provide interim data of a single-arm trial in the same population [study 1540 group 6]. The MAH should investigate biomarkers in order to confirm that PD-L1 expression is not predictive of efficacy. The study should be conducted according to an agreed protocol.	31st March 2023

Description	Due date
In order to confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation, the MAH should submit the final study report for Groups 1-3 in the phase 2 pivotal study 1540.	31st October 2022

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

LIBTAYO 350 mg concentrate for solution for infusion
cemiplimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 50 mg of cemiplimab.
Each vial contains 350 mg of cemiplimab in 7 ml.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine monohydrochloride monohydrate, L-proline, polysorbate 80, sucrose, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

concentrate for solution for infusion
350 mg/7 ml

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Regeneron Ireland DAC
Europa House, Harcourt Centre
Harcourt Street, Dublin 2, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1376/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

LIBTAYO 350 mg sterile concentrate
cemiplimab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

350 mg/7 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

LIBTAYO 350 mg concentrate for solution for infusion

cemiplimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the Patient Alert Card with you during treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What LIBTAYO is and what it is used for

LIBTAYO is an anti-cancer medicine that contains the active substance cemiplimab, which is a monoclonal antibody.

LIBTAYO is used in adults to treat a type of skin cancer called advanced cutaneous squamous cell carcinoma or CSCC.

LIBTAYO works by helping your immune system fight your cancer.

2. What you need to know before you are given LIBTAYO

You should not be given LIBTAYO if:
- you are allergic to cemiplimab or any of the other ingredients of this medicine (listed in section 6).
- If you think you may be allergic, or you are not sure, talk to your doctor before you are given LIBTAYO.

Warnings and precautions
Talk to your doctor or nurse before you are given LIBTAYO if:
- you have an autoimmune disease (a condition where the body attacks its own cells)
- you have had an organ transplant
- you have lung or breathing problems

- you have liver problems
- you have diabetes
- you have any other medical conditions.

If any of the above apply to you, or you are not sure, talk to your doctor or nurse before you are given LIBTAYO.

Look out for side effects
LIBTAYO can cause some serious side effects that you need to tell your doctor about immediately. You may have more than one side effect at the same time. These serious side effects include:

- Skin problems
- Lung problems (pneumonitis)
- Gut problems (colitis)
- Liver problems (hepatitis)
- Hormone gland problems - especially thyroid, pituitary, adrenal glands and the pancreas
- Kidney problems (nephritis and kidney failure)
- Infusion-related reactions
- Central nervous system problems (such as meningitis)
- Problems in other parts of the body.

Look out for these side effects while you are having LIBTAYO. See 'Possible side effects' section in section 4. If you have any of these effects, talk to your doctor immediately.
Your doctor may give you other medicines in order to stop more severe reactions and reduce your symptoms. Your doctor also may delay your next dose of LIBTAYO or stop your treatment.

Children and adolescents
LIBTAYO should not be used in children and adolescents below 18 years of age.

Other medicines and LIBTAYO
Tell your doctor if you are taking, have recently taken or might take any other medicines.
In particular, tell your doctor if you are taking or have ever taken any of the following medicines:

- a cancer medicine called idelalisib
- medicines that make your immune system weak - examples include corticosteroids, such as prednisone. These medicines may interfere with the effect of LIBTAYO. However, once you are treated with LIBTAYO, your doctor may give you corticosteroids to reduce the side effects that you may have with LIBTAYO.

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

- LIBTAYO can harm your unborn baby.
- Tell your doctor immediately if you become pregnant while you are being treated with LIBTAYO.
- If you are able to become pregnant, you must use an effective method of contraception to avoid becoming pregnant:
  - while you are being treated with LIBTAYO and
  - for at least 4 months after the last dose.
- Talk to your doctor about the contraception methods that you must use during this time.

Breast-feeding

- If you are breast-feeding or plan to breast-feed, ask your doctor for advice before you are given this medicine.
- Do not breast-feed while you are being treated with LIBTAYO and for at least 4 months after the last dose.
- It is not known if LIBTAYO passes into your breast milk.

Driving and using machines
LIBTAYO has no or minor influence on your ability to drive and use machines. If you feel tired, do not drive or use machines until you feel better.

3. How you are given LIBTAYO

- LIBTAYO will be given to you in a hospital or clinic - supervised by a doctor experienced in cancer treatment.
- LIBTAYO is given as a drip into a vein (intravenous infusion).
- The infusion will last about 30 minutes.
- LIBTAYO is usually given every 3 weeks.

How much you will receive
The recommended dose of LIBTAYO is 350 mg.
Your doctor will decide how much LIBTAYO you will receive and how many treatments you will need.
Your doctor will test your blood for certain side effects during your treatment.

If you miss an appointment
Call your doctor as soon as possible to make another appointment. It is very important that you do not miss a dose of this medicine.

If you stop receiving LIBTAYO
Do not stop treatment of LIBTAYO unless you have discussed this with your doctor. This is because stopping your treatment may stop the effect of the medicine.

Patient Alert Card
The information in this Package Leaflet can be found in the Patient Alert Card you have been given by your doctor. It is important that you keep this Patient Alert Card and show it to your partner or caregivers.
If you have any questions about your treatment, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

LIBTAYO acts on your immune system and may cause inflammation in parts of your body (see the conditions listed in 'Look out for side effects' in section 2). Inflammation may cause serious damage to your body. Some inflammatory conditions may also lead to death and need treatment, or you may need to stop treatment with LIBTAYO.

Seek urgent medical attention if you have any of the following signs or symptoms, or if they get worse:

- **Skin problems** such as rash or itching, skin blistering and ulcers in mouth or other mucous membrane.

- **Lung problems (pneumonitis)** such as new or worsening cough, being short of breath and chest pain.
- **Gut problems (colitis)** such as frequent diarrhoea often with blood or mucus, more bowel movements than usual, stools that are black or tarry, and severe stomach (abdomen) pain or tenderness.
- **Liver problems (hepatitis)** such as yellowing of your skin or the whites of your eyes, severe nausea or vomiting, pain on right side of your stomach (abdomen), feeling sleepy, dark urine (the colour of tea), bleeding or bruising more easily than normal and feeling less hungry than usual.
- **Hormone gland problems** such as headache that will not go away or unusual headaches, fast heartbeat, increased sweating, feeling cold, very tired, dizzy or fainting, weight gain or weight loss, feeling more hungry or thirsty than usual, hair loss, constipation, your voice gets deeper, very low blood pressure, passing water more often than usual, nausea or vomiting, stomach (abdomen) pain, changes in mood or behaviour (such as decreased sex drive, being irritable or forgetful).
- **Type 1 diabetes** that may include feeling more hungry or thirsty than usual, needing to urinate more often, weight loss, and feeling tired.
- **Kidney problems (nephritis and kidney failure)** such as passing water less often than usual, passing blood, swollen ankles and feeling less hungry than normal.
- **Infusion-related reactions (sometimes can be severe or life-threatening)** such as chills, shaking or fever, itching or rash, flushing or swollen face, being short of breath or wheezing, feeling dizzy or feel like passing out and back or neck pain.
- **Problems in other parts of the body** such as headache or stiff neck, fever, feeling tired or weak, confusion, memory problems or feeling sleepy, fits (seizures), seeing or hearing things that are not really there (hallucinations), changes in eyesight, eye pain or redness, severe muscle weakness, changes in heartbeat, such as beating fast or seeming to skip a beat or pounding sensation and bruises on the skin or bleeding.

The following side effects have been reported in clinical trials of patients with CSCC:
Very common (may affect more than 1 in 10 people):

- feeling tired
- rash, itching
- diarrhoea (loose stools).

Common (may affect up to 1 in 10 people):

- increased liver enzymes in blood, abnormal kidney function test
- thyroid gland problems
- cough, inflammation of the lungs
- joint pain, swelling, polyarthritis and joint effusion
- infusion-related reactions
- inflammation of the mouth
- inflammation of the liver
- muscle pain.

Uncommon (may affect up to 1 in 100 people):

- inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired or chest pain
- inflammation of the covering of the heart
- inflammation of the kidneys
- inflammation of the pituitary gland situated at the base of the brain; decreased secretion of hormones produced by the adrenal glands; inflammation of the thyroid
- type 1 diabetes that may include feeling more hungry or thirsty than usual, needing to urinate more often, weight loss, and feeling tired

- a temporary inflammation of the nerves that cause pain, weakness, and paralysis in the extremities; a condition in which the muscles become weak and tire easily
- inflammation of brain and spinal cord membranes usually caused by infection
- dryness in many parts of the body, from mouth to eyes, nose, throat and the top layers of skin
- eye pain, irritation, itchiness or redness; uncomfortable sensitivity to light
- inflammation of the nerves causing tingling, numbness, weakness or burning pain of the arms or legs
- bruises on the skin or bleeding.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store LIBTAYO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original container in order to protect from light.
From time of preparation by diluting in an intravenous bag, LIBTAYO can be stored before use for no more than 8 hours at temperatures up to 25°C, and no more than 24 hours in a refrigerator (2°C to 8°C). If refrigerated, the vials and/or intravenous bags must be allowed to reach room temperature prior to use.

Do not store any unused portion of the infusion solution for re-use. Any unused portion of the infusion solution should not be re-used and should be disposed in accordance with local requirements.

6. Contents of the pack and other information

What LIBTAYO contains
The active substance is cemiplimab:
- One ml of concentrate contains 50 mg of cemiplimab.
- Each vial contains 350 mg cemiplimab in 7 ml of concentrate.

The other ingredients are L-Histidine, L-Histidine monohydrochloride monohydrate, L-proline, sucrose, polysorbate 80 and water for injections.

What LIBTAYO looks like and contents of the pack
LIBTAYO concentrate for solution for infusion (sterile concentrate) is supplied as a clear to slightly opalescent, colourless to pale yellow sterile solution that may contain trace amounts of translucent to white particles.

Each carton contains 1 glass vial with 7 ml of concentrate.

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Manufacturer
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This leaflet was last revised in June 2019.

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Instructions for use

Preparation

- Visually inspect the medicinal product for particulate matter and discoloration prior to administration. LIBTAYO is a clear to slightly opalescent, colourless to pale yellow solution that may contain trace amounts of translucent to white particles.
- Discard the vial if the solution is cloudy, discoloured or contains extraneous particulate matter other than trace amounts of translucent-to-white particles.
- Do not shake the vial.
- Withdraw 7 ml (350 mg) from the vial of LIBTAYO and transfer into an intravenous infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection. Mix the diluted solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should be between 1 mg/ml to 20 mg/ml.
- LIBTAYO is for single use only. Dispose of any unused medicinal product or waste material in accordance with local requirements.

Storage of diluted solution

LIBTAYO does not contain a preservative.
Once prepared, administer the diluted solution immediately. If diluted solution is not administered immediately, it may be stored temporarily either:

- at room temperature up to 25°C for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion solution in the intravenous container and time for administration of the infusion

Or

- under refrigeration at 2°C to 8°C for no more than 24 hours from the time of infusion preparation. Allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

Administration

- LIBTAYO is for intravenous use. It must be administered by intravenous infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding, in-line or add-on filter (0.2 micron to 5 micron pore size).
- Do not co-administer other medicines through the same infusion line.