PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrLIBTAYO™

Cemiplimab

Concentrate for solution for infusion (50mg/mL)

Antineoplastic Agent, Monoclonal Antibody

LIBTAYO™, 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

has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for LIBTAYO please refer to Health Canada's Notice of Compliance with conditions - drug products web site.

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Distributed by Sanofi Genzyme,
a division of sanofi-aventis Canada Inc.
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Submission Control No: 218718

This product has been authorized under the Notice of Compliance with Conditions (NOC/c) for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications;
- Action and Clinical Pharmacology;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions /index-eng.php

PART I: HEALTH PROFESSIONAL INFORMATION

NOC/c

1 INDICATIONS

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

Marketing authorization with conditions is based on tumour response rate and durability of response. An improvement in overall survival (OS) or progression free survival (PFS) has not yet been established in this single arm study (see CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of LIBTAYO in pediatric patients has not been established.

1.2 Geriatrics

Geriatrics (>75 years of age): No overall differences in efficacy were observed between younger patients (<75 years of age) and elderly patients (≥75 years of age) (see WARNINGS and PRECAUTIONS, Geriatrics).

NOC/c

2 CONTRAINDICATIONS

LIBTAYO (cemiplimab) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION and PACKAGING section of the Product Monograph.

NOC/c

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

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

3.2 Recommended Dose and Dosage Adjustment

The recommended dose of LIBTAYO is 350 mg every three (3) weeks administered as an intravenous infusion over 30 minutes until symptomatic disease progression or unacceptable toxicity.

Alternatively, a dose of 3mg/kg every two (2) weeks administered as an intravenous infusion over 30 minutes may be considered in patients with a low body weight at the discretion of the treating healthcare professional (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Treatment may be continued through initial measurable disease progression until symptomatic disease progression or unacceptable toxicity.

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.

Table 1: Recommended Treatment Modifications for Adverse Reactions

<table>
<tr><th>Adverse Reaction</th><th>Severity[a]</th><th>Dose modification</th><th>Additional Intervention</th></tr>
<tr><td rowspan="3">Pneumonitis</td><td rowspan="2">Grade 2</td><td>Withhold LIBTAYO</td><td>Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper</td></tr>
<tr><td colspan="2">Resume LIBTAYO if pneumonitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent</td></tr>
<tr><td>Grade 3 or 4
or
recurrent Grade 2</td><td>Permanently discontinue LIBTAYO</td><td>Initial dose of 2 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by a taper</td></tr>
<tr><td rowspan="2">Colitis</td><td rowspan="2">Grade 2 or 3</td><td>Withhold LIBTAYO</td><td>Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper</td></tr>
<tr><td colspan="2">Resume LIBTAYO if colitis or diarrhea improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent</td></tr>
</table>

Adverse Reaction	Severity[a]	Dose modification	Additional Intervention
	Grade 4 or recurrent Grade 3	Permanently discontinue LIBTAYO	Initial dose of 1 mg/kg/day 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 mg/kg/day 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 LIBTAYO	Initial dose of 1 mg/kg/day 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 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
		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	

Adverse Reaction	Severity[a]	Dose modification	Additional Intervention
Adrenal insufficiency	Grade 2 to 4	Withhold LIBTAYO	Initial dose of 1 mg/kg/day 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 (hyperglycemia)	Withhold LIBTAYO	Initiate treatment with anti-hyperglycemics 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 mg/kg/day 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 LIBTAYO	Initial dose of 1 mg/kg/day 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 mg/kg/day 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	

Adverse Reaction	Severity[a]	Dose modification	Additional Intervention
	Grade 3 or 4 (excluding endocrinopathies) or recurrent Grade 2	Permanently discontinue LIBTAYO	Initiate symptomatic management immediately, including initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
Nephritis	Grade 2	Withhold LIBTAYO	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
		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 LIBTAYO	Initial dose of 1 mg/kg/day 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,	Moderate or severe 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	

Adverse Reaction	Severity[a]	Dose modification	Additional Intervention
chronic inflammatory demyelinating polyradiculoneuropathy, central nervous system inflammation, autoimmune myocarditis, and immune thrombocytopenic purpura, myalgia, Sjogren's syndrome, vasculitis, myasthenia gravis)[b]	• Life-threatening 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 LIBTAYO	Initial dose of 1 mg/kg/day 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 LIBTAYO	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.
[a] Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).
[b] Observed with LIBTAYO or with other anti-PD-1/PD-L1 monoclonal antibodies

3.3 Special Populations

Pediatrics:

The safety and efficacy of LIBTAYO in pediatric patients has not been established.

Elderly:

No dose adjustment is recommended for elderly patients (≥ 75 years) (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Renal Impairment:

No formal studies of LIBTAYO in patients with renal impairment have been conducted.

Based on a population pharmacokinetic analysis, no dose adjustment of LIBTAYO is recommended for patients with mild (CLcr 60-89 mL/min, n=197 patients) or moderate (CLcr 30 to <60 mL/min, n=90 patients) renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Based on a population pharmacokinetic analysis, which included 4 patients with severe renal impairment, a 30% lower exposure to cemiplimab was observed. There are limited data available on the safety and efficacy of LIBTAYO in patients with severe renal impairment (CLcr <30 mL/min). Data are not sufficient for drawing a conclusion on patients with severe renal impairment.

Hepatic Impairment:

No formal studies of LIBTAYO in patients with hepatic impairment have been conducted.

Based on a population pharmacokinetic analysis, which included 5 patients with mild hepatic impairment (total bilirubin [TB] >1.0 to 1.5 times the upper limit of normal [ULN] or AST >ULN), no differences in exposure were observed in patients who did not receive any dose adjustment during the clinical trials.

LIBTAYO has not been studied in patients with moderate (TB >1.5 to 3.0 times ULN and any AST) or severe (TB >3 times ULN and any AST) hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY).

3.4 Preparation and Administration

Preparation and Reconstitution

- Visually inspect drug product for particulate matter and discolouration prior to administration. LIBTAYO is 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 the required volume from the vial(s) of LIBTAYO and transfer into an intravenous (IV) infusion bag containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Mix diluted solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should be between 1mg/mL to 20mg/mL
- LIBTAYO is for single use only. Dispose of any unused medicinal product or waste material in accordance with local requirements
- No compatibility studies have been performed. Do not mix with other medicinal products.

Storage 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 IV 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
- Do not shake

Administration

- LIBTAYO must be administered by intravenous infusion over 30 minutes through an intravenous line containing a sterile, in-line or add-on filter (0.2 micron to 5 micron pore size)
- Do not co-administer with other drugs through the same infusion line.

3.5 Missed Dose

If a planned dose of LIBTAYO is missed, it should be administered as soon as possible; do not wait until the next planned dose. Maintain the planned schedule of administration of subsequent doses.

4 OVERDOSAGE

No cases of overdose with LIBTAYO have been reported.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous (IV) Infusion	Sterile solution for infusion/ 350mg cemiplimab / 7mL (10mL single use vial) 250mg cemiplimab / 5mL (10mL single use vial)	L-Histidine, L-Histidine Monohydrochloride Monohydrate, Sucrose, L-Proline, Polysorbate 80, Water for Injection

5.1 Dosage Form Description

LIBTAYO is a clear to slightly opalescent, colorless to pale yellow sterile solution with a pH of 6.0 that may contain trace amounts of translucent to white particles.

5.2 Packaging

LIBTAYO is provided in a 10mL glass vial with a 20mm finish made of clear Type 1 glass, equipped with a 20mm grey chlorobutyl elastomeric liquid stopper. The 350mg vial has a violet flip-off button and the 250mg vial has a light green flip-off button.

NOC/ 6 WARNINGS AND PRECAUTIONS

6.1 General

LIBTAYO should be administered under the supervision of health care practitioners experienced in the treatment of cancer.

Solid organ transplant rejection has been reported in patients treated with other PD-1 inhibitors. Patients with history of solid organ transplant were excluded from LIBTAYO clinical studies. Treatment with LIBTAYO may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with LIBTAYO versus the risk of possible organ rejection in these patients.

6.2 Driving and Operating Machinery

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

6.3 Immune

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis, defined as requiring use of corticosteroids with no clear alternate etiology, including fatal cases, has been observed in patients receiving LIBTAYO (see ADVERSE REACTIONS).

Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and manage with treatment modifications and corticosteroids.

Administer corticosteroids at an initial dose of 1 to 2 mg/kg/day (Grade 2) or 2 to 4 mg/kg/day (Grade 3 or greater or recurrent moderate Grade 2) prednisone or equivalent, followed by a corticosteroid taper.

Withhold LIBTAYO for moderate (Grade 2) pneumonitis. Resume LIBTAYO if pneumonitis improves and remains at Grade 0-1 after corticosteroid taper to less than 10 mg/day prednisone or equivalent. Permanently discontinue for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis (see DOSAGE AND ADMINISTRATION).

Immune-mediated pneumonitis occurred in 13 (2.4%) of 534 patients receiving LIBTAYO including 1 (0.2%) patient with Grade 5, and 4 (0.7%) patients with Grade 3 pneumonitis. Immune-mediated pneumonitis led to permanent discontinuation of LIBTAYO in 7 (1.3%) of 534 patients. Among the 13 patients with immune-mediated pneumonitis, the median time to onset was 1.8 months (range: 7 days to 7.4 months) and the median duration of pneumonitis was 25 days (range: 5 days to 4.9 months). Eleven patients (2.1%) received high-dose corticosteroids for a median of 7 days (range: 1 day to 4.7 months). Resolution of pneumonitis had occurred in 9 (69.2%) of the 13 patients at the time of data cut-off.

Immune-Mediated Colitis

Immune-mediated diarrhea or colitis, defined as requiring use of corticosteroids with no clear alternate etiology, has been observed in patients receiving LIBTAYO (see ADVERSE REACTIONS).

Monitor patients for signs and symptoms of diarrhea or colitis and manage with treatment modifications, anti-diarrheal agents, and corticosteroids.

Administer corticosteroids at an initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper for Grade 2 or greater diarrhea or colitis.

Withhold LIBTAYO for moderate or severe (Grade 2 or 3) diarrhea or colitis until resolution. Resume LIBTAYO if diarrhea or colitis improves and remains at Grade 0 to 1 after corticosteroid taper to less than 10 mg/day prednisone or equivalent. Permanently discontinue LIBTAYO for life-threatening (Grade 4), or for recurrent severe (Grade 3) diarrhea or colitis (see DOSAGE AND ADMINISTRATION).

Immune-mediated diarrhea or colitis occurred in 5 (0.9%) of 534 patients receiving LIBTAYO including 2 (0.4%) with Grade 3 immune-mediated diarrhea or colitis. Immune-mediated diarrhea or colitis led to permanent discontinuation of LIBTAYO in 1 (0.2%) patient. Among the 5 patients with immune-mediated diarrhea or colitis, the median time to onset was 3.8 months (range: 15 days to 4.5 months) and the median duration of immune-mediated diarrhea or colitis was 23 days (range: 4 days to 3.0 months). Three patients (0.6%) with immune-mediated diarrhea or colitis received high-dose corticosteroids for a median of 28 days (range: 12 days to 2.0 months). Resolution of immune-mediated diarrhea or colitis had occurred in 3 (60%) of the 5 patients at the time of data cut-off.

Immune-Mediated Hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids with no clear alternate etiology, including fatal cases, has been observed in patients receiving LIBTAYO (see ADVERSE REACTIONS).

Monitor patients for abnormal liver tests prior to and periodically during treatment, and manage with treatment modifications and corticosteroids.

Administer corticosteroids at an initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper for Grade 2 (AST or ALT >3 and ≤5xULN or total bilirubin >1.5 and ≤3xULN) or greater hepatitis.

Withhold LIBTAYO for moderate (Grade 2) hepatitis until resolution. Resume LIBTAYO if

hepatitis improves and remains at Grade 0 to 1 after corticosteroid taper to less than 10 mg/day prednisone or equivalent, or returns to baseline AST or ALT after completion of corticosteroid taper. Permanently discontinue for severe (Grade 3 with AST or ALT >5xULN or total bilirubin >3xULN) or life threatening (Grade 4) immune-mediated hepatitis (see DOSAGE AND ADMINISTRATION).

Immune-mediated hepatitis occurred in 11 (2.1%) of 534 patients receiving LIBTAYO including 1 (0.2%) patient with Grade 5, 1 (0.2%) with Grade 4, and 9 (1.7%) with Grade 3 immune-mediated hepatitis. Immune-mediated hepatitis led to permanent discontinuation of LIBTAYO in 0.9% (5/534) of patients. Among the 11 patients with immune-mediated 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 to2.7 months). Ten (1.9%) patients with immune-mediated 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-Mediated Endocrinopathies

Immune-mediated endocrinopathies have been observed in patients receiving LIBTAYO (see ADVERSE REACTIONS).

Thyroid Disorders (Hypothyroidism/Hyperthyroidism)

Immune-mediated thyroid disorders have been observed in patients receiving LIBTAYO. Thyroid disorders can occur at any time during the treatment.

Monitor patients for changes in thyroid function at the start of the treatment, periodically during treatment, and as indicated based on clinical evaluation. Manage patients with hormone replacement therapy (if indicated) and treatment modifications. Initiate medical management for control of hyperthyroidism.

Withhold LIBTAYO for severe (Grade 3) or life-threatening (Grade 4) thyroid disorders. Resume LIBTAYO when thyroid disorders returns to Grade 0 to 1 or is otherwise clinically stable (see DOSAGE AND ADMINISTRATION).

Hypothyroidism

Hypothyroidism occurred in 32 (6.0%) of 534 patients receiving LIBTAYO including 1 (0.2%) patient with Grade 3 immune-mediated hypothyroidism. No patient discontinued LIBTAYO due to hypothyroidism. Among the 32 patients with immune-mediated hypothyroidism, the median time to onset was 4.0 months (range: 15 days to 13.7 months) and the median duration was 5.2 months (range: 1 day to 13.4 months). Immune-mediated hypothyroidism resolved in 3 (9.4%) of the 32 patients.

Hyperthyroidism

Hyperthyroidism occurred in 8 (1.5%) of 534 patients receiving LIBTAYO including 1 (0.2%) patient with Grade 3 hyperthyroidism. No patient discontinued LIBTAYO due to hyperthyroidism. Among the 8 patients with hyperthyroidism, the median time to onset was 1.6 months (range: 28 days to 5.7 months) and the median duration was 1.4 months (range: 8 days to 4.7 months). Hyperthyroidism resolved in 3 (37.5%) of the 8 patients.

Hypophysitis

Immune-mediated hypophysitis has been observed in patients receiving LIBTAYO.

Monitor patients for signs and symptoms of hypophysitis and manage with treatment modifications, corticosteroids at an initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper and hormone replacement, as clinically indicated.

Withhold LIBTAYO for moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Resume LIBTAYO if hypophysitis improves and remains at Grade 0 to 1 after corticosteroid taper to less than 10 mg/day prednisone or equivalent or is otherwise clinically stable (see DOSAGE AND ADMINISTATION).

Immune-mediated hypophysitis occurred in 1 (0.2%) of 534 patients receiving LIBTAYO. The event was Grade 3 hypophysitis.

Adrenal Insufficiency

Adrenal insufficiency has been observed in patients receiving LIBTAYO.

Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment and manage with treatment modifications, corticosteroids at an initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper and hormone replacement, as clinically indicated.

Withhold LIBTAYO for moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Resume LIBTAYO if adrenal insufficiency improves and remains at Grade 0 to 1 after corticosteroid taper to less than 10 mg/day prednisone or equivalent or is otherwise clinically stable (see DOSAGE AND ADMINISTRATION).

Adrenal insufficiency occurred in 2 (0.4%) of 534 patients receiving LIBTAYO including 1 (0.2%) patient with Grade 3 adrenal insufficiency. Adrenal insufficiency did not lead to permanent discontinuation of LIBTAYO in any patients. Among the 2 patients with adrenal insufficiency, the median time to onset was 10.9 months (range: 10.4 months 11.5 months) and the median duration was 3.4 months (range: 1.8 months to 5.1 months). One of the 2 patients was treated with systemic corticosteroids. The patient received high-dose corticosteroids for 1 day.

Type 1 Diabetes Mellitus

Immune-mediated type 1 diabetes mellitus, including diabetic ketoacidosis, has been observed in patients receiving LIBTAYO.

Monitor patients for hyperglycemia and signs and symptoms of diabetes and manage with oral anti-hyperglycemics or insulin and treatment modifications.

Withhold LIBTAYO and administer anti-hyperglycemics or insulin in patients with severe or life-threatening (Grade ≥ 3) hyperglycemia. Resume LIBTAYO when metabolic control is achieved on insulin replacement or anti hyperglycemics (see DOSAGE AND ADMINISTRATION).

New onset type 1 diabetes mellitus occurred in 4 (0.7%) of 534 patients including 2 (0.4%) patients with Grade 4 and 2 (0.4%) patients with Grade 3 hyperglycemia. Type 1 diabetes

mellitus led to permanent discontinuation of LIBTAYO in 1 patient. 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-Mediated Skin Adverse Reactions

Immune-mediated skin adverse reactions, defined as requiring use of corticosteroids with no clear alternate etiology, including rash, erythema multiforme, pemphigoid, and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (some cases with fatal outcome) have been observed (see ADVERSE REACTIONS).

Monitor patients for signs and symptoms of suspected severe skin reactions and exclude other causes. Manage patients with treatment modifications and corticosteroids at an initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper for Grade 2 lasting longer than 1 week, severe (Grade 3) or life-threatening (Grade 4) skin adverse reaction.

Withhold LIBTAYO for Grade 2 lasting longer than 1 week or severe (Grade 3) skin adverse reaction. Resume if skin adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to less than 10 mg/day prednisone or equivalent. For symptoms or signs of SJS or TEN, withhold LIBTAYO and refer the patient for specialized care for assessment and treatment. Permanently discontinue LIBTAYO for life-threatening (Grade 4) skin adverse reaction or if SJS or TEN is confirmed (see DOSAGE AND ADMINISTRATION).

Cases of SJS/TEN/stomatitis including fatal TEN occurred following 1 dose of LIBTAYO in patients with prior exposure to idelalisib, who were participating in a clinical trial evaluating LIBTAYO in Non Hodgkins Lymphoma (NHL), and who had recent exposure to sulfa containing antibiotics. Two patients experienced fatal mucocutaneous toxicity after a single dose of cemiplimab monotherapy, and a third patient developed myositis and myasthenia gravis following 2 doses of cemiplimab. Manage patients immediately with treatment modifications and corticosteroids as described above.

Immune-mediated skin adverse reactions occurred in 9 (1.7%) of 534 patients receiving LIBTAYO including 6 (1.1%) with Grade 3. Immune-mediated skin adverse reactions did not lead to permanent discontinuation of LIBTAYO in any patient. Among the 9 patients with immune-mediated skin adverse reactions, the median time to onset was 1.1 month (range: 2 days to 3.7 months) and the median duration was 2.3 months (range: 29 days to 9.2 months). Eight patients (1.5%) with immune-mediated skin adverse reactions received high-dose corticosteroids for a median of 13.5 days (range: 7 days to 2.5 months). Resolution had occurred in 6 (66.7%) of 9 patients at the time of data cut-off.

Immune-Mediated Nephritis

Immune-mediated nephritis, defined as requiring use of corticosteroids with no clear alternate etiology, has been observed in patients receiving LIBTAYO (see ADVERSE REACTIONS).

Monitor patients for changes in renal function. Manage patients with treatment modifications and corticosteroids at an initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper.

Withhold LIBTAYO for Grade 2. Resume LIBTAYO if nephritis improves and remains at Grade 0 to 1 after corticosteroid taper to less than 10 mg/day prednisone or equivalent. Permanently

discontinue for severe (Grade 3) or life-threatening (Grade 4) nephritis (see DOSAGE AND ADMINISTRATION).

Immune-mediated nephritis occurred in 3 (0.6%) of 534 patients receiving LIBTAYO including 2 (0.4%) patients with Grade 3 immune-mediated nephritis. Immune-mediated nephritis led to permanent discontinuation of LIBTAYO in 1 (0.2%) patient. Among the 3 patients with immune-mediated 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 (0.4%) patients with immune-mediated 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 3 patients at the time of data cut-off.

Other Immune-Mediated Adverse Reactions

Severe and fatal immune-mediated adverse reactions have been observed with LIBTAYO (see ADVERSE REACTIONS). These immune-mediated reactions may involve any organ system. Most immune-mediated reactions initially manifest during treatment with LIBTAYO; however, immune-mediated adverse reactions can occur after discontinuation of LIBTAYO.

For suspected immune-mediated adverse reactions, evaluate to confirm an immune-mediated adverse reaction and to exclude other causes. Manage with treatment modifications, hormone replacement therapy (if clinically indicated), and corticosteroids.

Depending upon the severity of the adverse reaction, withhold or permanently discontinue LIBTAYO, administer corticosteroids at an initial dose of 1 to 2 mg/kg/day prednisone or equivalent, and if appropriate, initiate hormone replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper. Resume treatment with LIBTAYO if other immune-mediated adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to less than 10 mg/day prednisone or equivalent. Permanently discontinue LIBTAYO for life-threatening adverse reaction (excluding endocrinopathies), or recurrent severe (Grade 3) immune-mediated adverse reaction, or persistent Grade 2 or 3 immune-mediated adverse reaction lasting 12 weeks or longer (excluding endocrinopathies), or inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks (see DOSAGE AND ADMINISTRATION).

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% of 534 patients treated with LIBTAYO: 2 (0.4%) meningitis (1 Grade 4 and 1 Grade 3), 1 (0.2%) paraneoplastic encephalomyelitis (Grade 5), 1 (0.2%) arthritis (Grade 3), 1 (0.2%) Guillain-Barre syndrome (Grade 3), 1 (0.2%) encephalitis (Grade 3), 1 (0.2%) chronic inflammatory demyelinating polyradiculoneuropathy (Grade 2), 1 (0.2%) central nervous system inflammation (Grade 2), 1 (0.2%) autoimmune myocarditis (Grade 3), 1 (0.2%) immune thrombocytopenic purpura (Grade 2), 2 (0.4%) myalgia (Grade 3), 1 (0.2%) Sjogren's syndrome (Grade 2), 1 (0.2%) vasculitis (Grade 2), and 1 (0.2%) myasthenia gravis (Grade 2). An additional event of Grade 4 myasthenia gravis occurred in a patient with prior exposure to idelalisib participating in a clinical trial evaluating LIBTAYO in Non-Hodgkins Lymphoma (NHL). The patient also experienced myositis.

Infusion-Related Reactions

LIBTAYO can cause severe or life-threatening infusion-related reactions (see ADVERSE REACTIONS).

Monitor patients for signs and symptoms of infusion-related reactions and manage with treatment modifications and corticosteroids.

Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue LIBTAYO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions (see DOSAGE AND ADMINISTRATION).

Infusion-related reactions occurred in 48 (9.0%) of 534 patients treated with LIBTAYO, including 1 (0.2%) patient with Grade 3 infusion-related reaction. Infusion-related reaction led to permanent discontinuation of LIBTAYO in 2 (0.4%) patients. All 48 patients recovered from the infusion-related reactions.

6.4 Sexual Health

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 (see NON-CLINICAL TOXICOLOGY).

6.5 Special Populations

6.5.1 Pregnant Women

There are no available data on the use of cemiplimab in pregnant women. Blockade of PD-1/PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. Animal reproduction studies have not been conducted with cemiplimab (see NON-CLINICAL TOXICOLOGY).

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 fetus.

Cemiplimab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Effective contraception should be used during treatment with cemiplimab and for at least 4 months following the last dose of LIBTAYO.

6.5.2 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 newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue LIBTAYO therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Breast-feeding women should be advised not to breast-feed during treatment and for at least 4 months after the last dose due to the potential risks to newborns/infants.

6.5.3 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of LIBTAYO in pediatric patients has not been established.

6.5.4 Geriatrics

No overall differences in efficacy were observed between younger patients (≤75 years of age) and those ≥75 years of age. Of the 163 patients with metastatic or locally advanced CSCC who received LIBTAYO in clinical studies, 63.2% (103/163) were younger than 75 years.

NOC/c

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

LIBTAYO has been evaluated as a monotherapy or as a combination therapy in 534 patients in two uncontrolled clinical studies (Study 1423 [Phase 1] and Study 1540 [Phase 2]). This included 98 patients with metastatic (nodal or distant) cutaneous squamous cell carcinoma (metastatic CSCC), 65 patients with locally advanced cutaneous squamous cell carcinoma (locally advanced CSCC) and 371 patients with other advanced solid malignancies.

Patients in both studies received LIBTAYO as an intravenous infusion over 30 minutes until unequivocal progression of disease, unacceptable toxicity or completion of planned treatment. Study 1423 was an open-label, multi-center study in 397 patients with a variety of advanced solid tumors. It included 16 patients with metastatic CSCC and 10 patients with locally advanced CSCC. Study 1540 was an open-label, multi-center study that had enrolled 137 patients with metastatic CSCC or locally advanced CSCC at the time of data cut-off. In the advanced CSCC patients, the median duration of exposure to LIBTAYO was 20 weeks (range: 3 days to 71 weeks).

Among the 534 patients treated with LIBTAYO in studies 1423 and 1540, 4 (0.7%) died due to treatment-related adverse events including one patient each who died from pneumonitis, hepatic failure, paraneoplastic encephalomyelitis and death of unknown cause.

The data described below reflect exposure to LIBTAYO in 163 patients with advanced CSCC (metastatic CSCC and locally advanced CSCC) in Study 1423 and Study 1540.

LIBTAYO was permanently discontinued due to adverse reactions in 8 (4.9%) patients; the only adverse reaction resulting in permanent discontinuation in more than 1 patient was pneumonitis. Serious adverse reactions occurred in 13 (8%) patients. The only serious adverse reaction that occurred in more than 1 patient was pneumonitis. There were no Grade 4 adverse reactions. The Grade 3 adverse reactions reported in more than 1 patient were hepatitis, rash, increased aspartate aminotransferase, and pneumonitis.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The study population characteristics were: median age of 71.0 years (range: 38 to 96), 84.7% male, 96.3% white, ECOG performance score of 0 (44.2%) or 1 (55.8%), and 42.9% of patients had at least 1 prior anti-cancer therapy, and 73.0% had prior radiotherapy.

Table 3: Adverse Reactions that Occurred in ≥1% of Advanced CSCC Patients Receiving LIBTAYO in Study 1423 and Study 1540

Adverse Reactions	**Cemiplimab N = 163**	
SOC/ PT	**All Grades N (%)**	**Grade 3-4 N (%)**
Skin and Subcutaneous Tissue Disorders		
Rash[a]	32 (19.6%)	2 (1.2%)
Pruritus[b]	17 (10.4%)	0
Gastrointestinal Disorders		
Diarrhoea[c]	20 (12.3%)	1 (0.6%)
General Disorders and Administration Site Conditions		
Fatigue[d]	34 (20.9%)	1 (0.6%)
Musculoskeletal and Connective Tissue Disorders		
Arthritis	2 (1.2%)	1 (0.6%)
Myalgia	4 (2.5%)	1 (0.6%)
Investigations		
Alanine Aminotransferase Increased	8 (4.9%)	1 (0.6%)
Aspartate Aminotransferase Increased	6 (3.7%)	2 (1.2%)
Blood Alkaline Phosphatase Increased	3 (1.8%)	0
Blood Creatinine Increased	3 (1.8%)	0
Endocrine Disorders		
Hypothyroidism	12 (7.4%)	0
Hyperthyroidism	3 (1.8%)	0
Respiratory, Thoracic, and Mediastinal Disorders		
Pneumonitis	6 (3.7%)	2 (1.2%)
Injury, Poisoning and Procedural Complications		
Infusion Related Reaction	7 (4.3%)	0
Hepatobiliary Disorders		
Hepatitis	3 (1.8%)	3 (1.8%)

[a] Rash is a composite term that includes rash maculo-papular, rash, dermatitis, rash generalized, dermatitis bullous, drug eruption, erythema, rash erythematous, rash macular, rash pruritic, and skin reaction.

[b] Pruritus is a composite term that includes pruritus and pruritus allergic.
[c] Diarrhea is a composite term that includes diarrhea and colitis.
[d] Fatigue is a composite term that includes fatigue and asthenia.

7.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with LIBTAYO. Five out of 398 patients 5/398 [1.3%] administered cemiplimab developed treatment emergent antibodies, with 1/398 patients [0.3%] exhibiting persistent antibody responses.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay as well as other factors. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cemiplimab with the incidence of antibodies to other products may be misleading.

7.4 Less Common Clinical Trial Adverse Reactions

Table 4: Adverse Reactions that Occurred in ≤1% of Advanced CSCC Patients Receiving LIBTAYO in Study 1423 and Study 1540

Adverse Reactions	**Cemiplimab N = 163**	
SOC/ PT	**All Grades N (%)**	**Grade 3-4 N (%)**
Musculoskeletal and Connective Tissue Disorders		
Sjogren's Syndrome	1 (0.6%)	0
Endocrine Disorders		
Adrenal Insufficiency	1 (0.6%)	1 (0.6%)
Hypophysitis	1 (0.6%)	1 (0.6%)
Nervous System Disorders		
Chronic Inflammatory Demyelinating Polyradiculoneuropathy	1 (0.6%)	0
Infections and Infestations		
Meningitis	1 (0.6%)	1 (0.6%)
Renal and Urinary Disorders		
Nephritis	1 (0.6%)	0
Cardiac Disorders		
Autoimmune Myocarditis	1 (0.6%)	1 (0.6%)

7.5 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 5: Selected Treatment-Emergent Laboratory Abnormalities in ≥15% of Advanced CSCC Patients Receiving LIBTAYO in Study 1423 and Study 1540*

Laboratory Tests	Any Grade (N=163) n/N (%)†	Grade 3-4 (N=163) n/N (%)†
Chemistry		
Aspartate aminotransferase increased	25/156 (16.0)	5/156 (3.2)
Creatinine increased	37/157 (23.6)	1/157 (0.6)
Hematology		
Anemia	66/157 (42.0)	3/157 (1.9)
Lymphopenia	65/157 (41.4)	11/157 (7.0)

* Treatment-emergent consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality
† Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter

8 DRUG INTERACTIONS

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

NOC/c

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Binding of the ligands PD-L1 and PD-L2, to PD-1 on T cells, inhibits T-cell proliferation and cytokine production. This pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

Cemiplimab is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that binds to programmed cell death 1 (PD-1) and blocks its interaction with PD-L1 and PD-L2, countering PD-1 mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

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

9.2 Pharmacokinetics

Concentration data were collected in 548 patients with various solid tumors, including 178 patients with CSCC, who received cemiplimab. At dosing regimens ranging from 1 mg/kg to 10 mg/kg administered intravenously every 2 weeks, the pharmacokinetics of cemiplimab were observed to be linear and dose proportional, over the dosing interval.

Based on a population pharmacokinetic analysis, with doses of 350 mg every 3 weeks, the median steady-state concentration of cemiplimab ranged between C_{max} of 168 mg/L and C_{trough}

of 61 mg/L. The 350 mg every 3 weeks regimen was not studied in patients who weighed below 54 kg. For the 3 mg/kg every 2 weeks regimen, the median steady-state concentration of cemiplimab ranged between C_{max} of 137 mg/L and C_{trough} of 68 mg/L. Steady-state exposure is achieved after approximately 4 months of treatment.

Table 6: Summary of Cemiplimab Pharmacokinetic Parameters in patients with various solid tumors following cemiplimab administration 350 mg every 3 weeks

	$C_{max,ss}$	$t_{½}$ (days)	$AUC_{6wk,ss}$	CL	Vd
Multiple Dose Mean*	168 mg/L	19.4	3890 mg*day/L	0.21 L/day	5.2 L

*Based on population pharmacokinetic model

Table 7: Summary of Cemiplimab Pharmacokinetic Parameters in patients with various solid tumors following cemiplimab administration 3 mg/kg every 2 weeks

	$C_{max,ss}$	$t_{½}$ (days)	AUC_{0-6wk}	CL	Vd
Multiple Dose Mean*	137 mg/L	19.4	3800 mg*day/L	0.21 L/day	5.2 L

*Based on population pharmacokinetic model

Distribution: Based on the population pharmacokinetic analysis, the volume of distribution of cemiplimab at steady-state is 5.2 L.

Elimination: Based on the population pharmacokinetic analysis, 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 within dosing interval half-life at steady state is estimated to be19.4 days.

9.3 Special Populations and Conditions

A population pharmacokinetic analysis suggests that the following factors have no clinically significant effect on the exposure of cemiplimab: age (<65 [27-64 years], n=260; ≥65 to <75, n=179; and ≥75 n=109), gender (n=217 females; n=331 males), body weight (30.9 to 147 kg [median body weight of 76.2 kg]), race (n=498 white; n=20 black; n=30 other), cancer type (n=178 CSCC patients and n=370 other solid tumors), albumin level (22 – 48 g/L*)*, and mild to moderate renal impairment (CLcr 60-89 mL/min, n=197 and CLcr 30 to <60 mL/min, n=90, respectively).

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Geriatrics*:* Of the 163 patients with metastatic CSCC and locally advanced CSCC treated with LIBTAYO, 63.2% (103/163) were younger than 75 years. Grade ≥3 treatment-related adverse reactions occurred in 8.7%% (9/103) of patients younger than 75 years and 18.3% (11/60) of patients 75 years or older. Grade ≥3 treatment-related Serious TEAEs occurred in 3.9% (4/103) of patients younger than 75 years, and 13.3% (8/60) of patients 75 years or older.

In the 108 patients evaluable for efficacy, the objective response rate in patients 65 years or older was 46.1% (35/76) and in patients 75 years or older was 44% (17/38).

No overall differences in efficacy were observed between younger patients and those ≥75 years of age.

Renal Insufficiency*:* The effect of renal impairment on the exposure of LIBTAYO was evaluated by a population pharmacokinetic 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 LIBTAYO were found between patients with mild to moderate renal impairment and patients with normal renal function. Given the limited data in patients with severe renal impairment included in the analysis (n=4), caution is required in the interpretation of the data on whether there are any clinically important differences in this population.

Hepatic Insufficiency*:* The effect of hepatic impairment on the exposure of LIBTAYO was evaluated by population pharmacokinetic analysis in patients (n=5) with mild hepatic impairment (total bilirubin [TB] greater than 1.0 to 1.5 times the upper limit of normal [ULN] and any AST). However, given the limited data available in patients with mild hepatic impairment included in the analysis (n=5), caution is required in the interpretation of the data on whether there are any clinically important differences in this population. LIBTAYO has not been studied in patients with moderate or severe hepatic impairment.

10 STORAGE, STABILITY AND DISPOSAL

Store LIBTAYO (cemiplimab) at 2 °C to 8 °C.

Protect LIBTAYO from light by storing in the original carton until time of use.

Do not freeze. Do not shake.

Do not use after the expiration date stamped in the carton and container label.

11 SPECIAL HANDLING INSTRUCTIONS

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

LIBTAYO™ 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

has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for LIBTAYO please refer to Health Canada's Notice of Compliance with conditions - drug products web site.

12 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Cemiplimab
Structure:	Cemiplimab (IgG4 isotype) is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a human kappa light chain.
Molecular formula:	$C_{6380}H_{9808}N_{1688}O_{2000}S_{44}$
Molecular mass:	143,567.1 Da
Physicochemical properties:	Clear to slightly opalescent, colourless to pale yellow liquid. Essentially free from visible particles

NOC/c

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Table 7: Summary of patient demographics for clinical trials in metastatic and locally advanced cutaneous squamous cell carcinoma

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
R2810-ONC-1423	Phase 1 First-in-human Open-label, repeat dose study with cemiplimab as monotherapy and combination therapy Adult patients (≥18 years old, males/females) with advanced solid malignancies	• 10mg/kg cemiplimab administered IV over 30 mins Q2W for 48 weeks • Cemiplimab 200mg dose IV infusion over 30 mins Q2W for 48 weeks • Cemiplimab at 1 or 3mg/kg administered IV over 30 minutes Q2W days for 48 weeks, alone or in combination with: radiotherapy, low-dose cyclophosphamide, or radiotherapy plus low-dose cyclophosphamide	397 patients (26 advanced CSCC patients)	61 (27-88) years	204 male 193 female
R2810-ONC-1540	Phase 2 Pivotal Study Non-randomized multicentre study, with cemiplimab 3mg/kg or 350mg as monotherapy Adult patients (≥18 years old, males/females) with mCSCC or laCSCC	• Treatment duration (Groups 1 and 2): 96 weeks (twelve 56-day [8-week] treatment cycles); tumor assessment at the end of each 8-week cycle Treatment duration (Group 3): 54 weeks (six 63-day [9-week] treatment cycles); tumor assessment at the end of each 9-week cycle • Post-treatment follow-up: approximately 6.4 months	137 patients	70 (38-96) years	117 male 20 female

The efficacy and safety of LIBTAYO in patients with metastatic (nodal or distant) cutaneous squamous cell carcinoma or locally advanced cutaneous squamous cell carcinoma who were not candidates for surgery were evaluated in two prospective clinical trials, Study 1423 and Study 1540. Study 1423 was an open-label, multi-center study in 397 patients with a variety of advanced solid tumors. It included 16 patients with metastatic CSCC and 10 patients with locally advanced CSCC who were treated with cemiplimab monotherapy. Study 1540 was an open-label, multi-center study that had enrolled 137 patients with metastatic CSCC or locally advanced CSCC at the time of data cut-off. Both studies excluded patients with autoimmune disease that required systemic therapy with immunosuppressant agents within 5 years; history of solid organ transplant; prior treatment with anti-PD-1/PD-L1 or other immune checkpoint inhibitor therapy; infection with HIV, hepatitis B or hepatitis C; or ECOG performance score ≥ 2.

Patients with anogenital squamous cell carcinoma (SCC) or SCCs arising on the dry red lip (vermillion) were not eligible.

Patients in both studies received LIBTAYO as an intravenous infusion over 30 minutes until unequivocal progression of disease, unacceptable toxicity or completion of planned treatment [3 mg/kg every 2 weeks for 48 weeks in Study 1423 or 96 weeks (Groups 1 and 2) in Study 1540 or 350 mg every 3 weeks for 54 weeks (Group 3) in Study 1540]. Patients could continue treatment beyond initial progression at the discretion of the investigator. If patients with locally advanced disease showed sufficient response to treatment, surgery with curative intent was permitted. Tumor response assessments were performed every 8 weeks. The primary endpoint 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 Tumors (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). Key secondary endpoint was duration of response (DOR). Other secondary endpoints were progression free survival (PFS), overall survival (OS), complete response rate (CRR) and EORTC QLQ-C30.

Results are presented as a combined analysis of 26 CSCC patients from Study 1423 (1 patient in the dose escalation cohort received cemiplimab 1mg/kg Q2W), and 82 patients from Study 1540 who received cemiplimab 3mg/kg every 2 weeks. Of these 108 patients, 75 were metastatic CSCC and 33 locally advanced CSCC with a median age of 71 years (range: 38 to 96). Thirty-eight (35.2%) patients were 75 years or older. Ninety-two (85.2%) patients were male, and 105 (97.2%) were White; the ECOG performance score was 0 (42.6%) or 1 (57.4%). Fifty per cent (50%) of patients had received at least one prior anti-cancer systemic therapy, 96.3% of patients had received prior cancer related surgery, and 78.7% of patients had received prior radiotherapy. Among patients with metastatic CSCC, 69.3% had distant metastases, and 30.7% had only nodal metastases.

Efficacy results are presented in Table 8 and Figure 1. Similar objective response rates (ORR) were observed in patients with metastatic CSCC (46.7%) and in patients with locally advanced CSCC (48.5%). At time of data cut-off, patients with advanced CSCC had been followed for a median duration of 8.9 months; the median duration of response (DOR) had not been reached Fifty-one (47.2%) patients achieved response, defined as complete response (CR) or partial response (PR). At the time of data cut-off, 4 of these responding patients had subsequent progression.

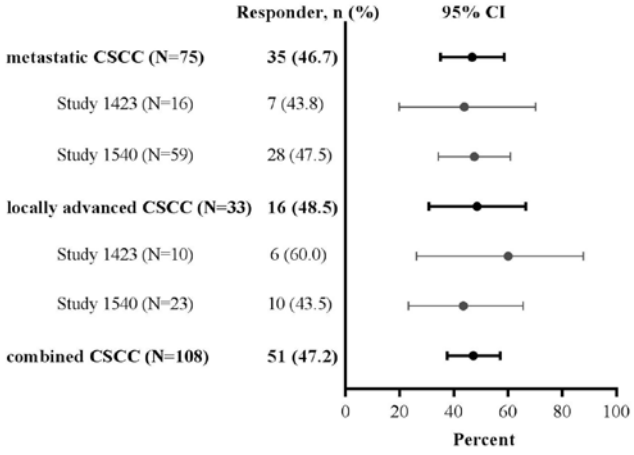
13.2 Study Results

Table 8: **Combined Efficacy Results for Study 1423 and Study 1540 – metastatic CSCC, locally advanced CSCC and combined CSCC**

Efficacy Endpoints[a]	**metastatic CSCC (N = 75)**	**locally advanced CSCC (N = 33)**	**combined CSCC (N = 108)**
Confirmed Objective Response Rate (ORR)			
ORR % 95% CI	46.7% (35.1%, 58.6%)	48.5% (30.8%, 66.5%)	47.2% (37.5%, 57.1%)
Complete response rate (CR)[b]	5.3%	0%	3.7%
Partial response rate (PR)	41.3%	48.5%	43.5%
Duration of Response (DOR) [c]			
Median (months)	NR	NR	NR
Range (months)	2.8 – 15.2+	1.0 – 12.9+	1.0 – 15.2+
Patients with DOR ≥ 6 months, %	60.0%	62.5%	60.8%
Time to Response (months)			
Median Range (months)	1.9 (1.7, 6.0)	3.7 (1.8, 7.6)	1.9 (1.7, 7.6)

CI: confidence interval; NR: Not reached; +: Denotes ongoing at last assessment
[a] Median duration of follow up: metastatic CSCC: 8.1 months; locally advanced CSCC: 10.2 months; combined CSCC: 8.9 months
[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] 41 of 51 responses are on-going at last assessment

Figure 1: **Objective Response rate Consistent across Studies and Populations**



14 NON-CLINICAL TOXICOLOGY

14.1 Repeat-Dose Toxicity

The safety of cemiplimab was evaluated in a 1-month and a 6-month repeat-dose toxicity studies in cynomolgus monkeys. The no-observed adverse effect level (NOAEL) was the highest dose administered in these studies (50 mg/kg/week).

14.2 Impairment on Fertility

In a 3-month repeat-dose fertility assessment study with sexually mature cynomolgus monkeys at the highest dose (50 mg/kg/week) tested, there were no cemiplimab-related effects on fertility assessment parameters (menstrual cycle, semen analysis, or testicular measurements) or in male or female reproductive organs.

14.3 Carcinogenesis

No carcinogenicity studies have been conducted with cemiplimab.

14.4 Genotoxicity

No genotoxicity studies have been conducted with cemiplimab.

14.5 Teratogenicity

Animal reproduction studies have not been conducted with cemiplimab.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

LIBTAYO

Cemiplimab, concentrate for solution for infusion

Read this carefully before you start taking **LIBTAYO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LIBTAYO**.

What is LIBTAYO used for?

LIBTAYO is a medicine used to treat a rare type of skin cancer which may or may not have spread called advanced cutaneous squamous cell carcinoma. Refer to the summary box below for additional detail.

For the following indication LIBTAYO has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- 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.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does LIBTAYO work?

LIBTAYO works by helping your immune system fight your cancer.

What are the ingredients in LIBTAYO?

Medicinal ingredients:	Cemiplimab
Non-medicinal ingredients:	L-histidine, L-histidine monohydrochloride monohydrate, L-proline, Polysorbate 80, Sucrose, Water for injection

LIBTAYO comes in the following dosage forms:
LIBTAYO comes in a 10mL glass vial containing either 250mg or 350mg of cemiplimab.

Do not use LIBTAYO if:
- You are allergic to cemiplimab or any of the other ingredients in this medicine. Talk to your health care professional if you are not sure.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LIBTAYO. Talk about any health conditions or problems you may have, including if you have:
- An autoimmune disease (a condition where your body attacks its own cells)
- Had an organ transplant
- Lung or breathing problems
- Liver problems
- Kidney problems
- Diabetes
- Any other medical conditions
- A history of taking idelalisib (a medication to treat cancer)

Other warnings you should know about:
Pregnancy:
- If you are pregnant, or are planning to have a baby, tell your healthcare professional before taking this medicine. You must not use LIBTAYO if you are pregnant unless your healthcare professional specifically recommends it.
- LIBTAYO can cause harm to your unborn baby.
- If you are a woman who could become pregnant, you must use effective birth control while you are being treated with LIBTAYO and for at least 4 months after your last dose.

Breast-feeding:
- If you are breast-feeding, or plan to breast-feed, tell your healthcare professional
- Do not breast-feed while receiving LIBTAYO and for at least 4 months after your last dose
- It is unknown if LIBTAYO passes into your breast milk. A risk to the breast-fed infant cannot be excluded

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

Driving and using machines
- It is not known whether LIBTAYO affects your ability to drive or use tools or machines. However, if you feel tired, do not drive or use tools or machines until you feel better.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take LIBTAYO:
- You will receive LIBTAYO in a hospital or clinic under the supervision of an experienced healthcare professional
- You will receive LIBTAYO as a drip into a vein (intravenous infusion)
- It will last about 30 minutes
- LIBTAYO is usually given every 3 weeks. Your doctor may choose to treat you with an every 2 week regimen if more appropriate for you.

Usual dose:
The recommended dose of LIBTAYO is 350 mg every 3 weeks or 3mg/kg every 2 weeks. 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.

Overdose:

If you think you have taken too much LIBTAYO, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss any appointments, call your healthcare professional as soon as possible to reschedule your appointment. It is very important that you do not miss a dose of this medicine.

What are possible side effects from using LIBTAYO?

These are not all the possible side effects that you may feel when taking LIBTAYO. If you experience any side effects not listed here, contact your healthcare professional.

The following side effects have been reported in clinical trials of patients with cutaneous squamous cell carcinoma (CSCC):

Very common (may affect more than 1 in 10 people)
- Feeling tired
- Rash
- Itching
- Diarrhea (loose stools)

Common (may affect up to 1 in 100 people)
- Increased liver enzymes in blood, abnormal kidney function test
- Thyroid gland problems
- Cough, inflammation of lungs
- Infusion related reactions
- Inflammation of the liver

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
Lung Problems (pneumonitis) Signs and symptoms may include: • New or worsening cough • Shortness of breath • Chest pain		√
Liver Problems (hepatitis) Signs and symptoms may include: • Yellowing of your skin or the whites of your eyes • Severe nausea or vomiting • Pain on the right side of your stomach area (abdomen) • Drowsiness • Dark urine (tea coloured) • Bleeding or bruising more easily than normal • Feeling less hungry than usual		√
Intestinal Problems (colitis) Signs and symptoms may include: • Diarrhea or more bowel movements than usual • Stools that are black, tarry, sticky, or have blood or mucous • Severe stomach area (abdomen) pain or tenderness		√
Hormone Gland Problems ((especially the thyroid, adrenals, pituitary and pancreas) Signs and symptoms may include • 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 • Urinating more than usual • Nausea • Vomiting • Stomach (abdomen) pain • Changes in mood or behavior (such as decreased sex drive, being irritable or forgetful)		√

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
Kidney Problems (nephritis and kidney failure) Signs and symptoms may include: • Decrease in the amount of urine • Blood in your urine • Swelling of your ankles • Feeling less hungry than usual		√
Skin Problems Signs of these problems may include: • Rash • Itching • Skin blistering • Ulcers in mouth or other mucous membranes		√
Infusion Related Reactions (sometimes can be severe or life-threatening) Signs and symptoms may include: • Chills or shaking • Fever • Itching or rash • Flushing or swollen face • Being short of breath or wheezing • Feeling dizzy or feeling like passing out • Back and/or neck pain		√
Problems in other parts of the body Signs and symptoms may include: • Changes in eyesight • Severe or persistent muscle or joint pains • Severe muscle weakness • Chest pain, shortness of breath, irregular heartbeat (myocarditis)		√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
LIBTAYO should not be used after the expiry date which is stated on the label and carton.

LIBTAYO should be stored in a refrigerator (2°C to 8°) in its original package to protect from light.

Do not freeze.

Do not shake.

From time of preparation by diluting in an intravenous (IV infusion) 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.

Keep out of reach and sight of children.

If you want more information about LIBTAYO:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the sanofi-aventis Canada website www.sanofi.ca, or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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