Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Cemiplimab

Proprietary Product Name: Libtayo

Sponsor: Sanofi-Aventis Australia Pty Ltd

November 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
AE	Adverse event
AR	Adverse reaction
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific Annex
AusPAR	Australian Public Assessment Report
BLA	Biologics license application (United States Food and Drug Administration)
CDR	Complementarity determining region(s)
CH	Constant region of the heavy chain
CHMP	Committee for Medicinal Products for Human Use (European Medicines Agency)
CHO	Chinese hamster ovary
CL	Constant region of the light chain
CMI	Consumer Medicines Information
CPD	Certified product details
CR	Complete response
CSCC	Cutaneous squamous cell carcinoma
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group (United States)
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency (European Union)

Abbreviation	Meaning
EU	European Union
Fc	Fragment crystallisable
FDA	Food and Drug Administration (United States)
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practices
IgG4	Immunoglobulin G4
irAR	Immune-related adverse reaction
iRR	Infusion related reaction
IV	Intravenous
laCSCC	Locally advanced cutaneous squamous cell carcinoma
M1	Metastasis category 1, distant metastatic disease
mAb	Monoclonal antibody
MAH	Marketing authorisation holder
mCSCC	Metastatic cutaneous squamous cell carcinoma
NCCN	National Comprehensive Cancer Network (United States)
NCI	National Cancer Institute (United States)
NDA	New drug applications
ORR	Objective response rate / overall response rate (used interchangeably)
OS	Overall survival
PD-1	Programmed cell death protein 1
PD-2	Programmed cell death protein 2
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression free survival
PI	Product Information

Abbreviation	Meaning
PK	Pharmacokinetic(s)
PR	Partial response
PSUR	Periodic Safety Update Report
Q2W	Every two weeks
Q3W	Every three weeks
RECIST	Response evaluation criteria in solid tumours
RMP	Risk management/minimisation Plan
SD	Stable disease
SmPC	Summary of product characteristics (European Union)
TGA	Therapeutic Goods Administration
TTR	Time to response
US(A)	United States (America)
VH	Variable region of the heavy chain
VL	Variable region of the light chain

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Product name:	Libtayo
Active ingredient:	Cemiplimab
Decision:	Approved for provisional registration
Date of decision:	2 July 2020
Date of entry onto ARTG:	17 July 2020
ARTG number:	320609
, *Black Triangle Scheme:*[1]	Yes As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration
Sponsor's name and address:	Sanofi-Aventis Pty Ltd 12-24 Talavera Road, Macquarie Park, NSW 2113
Dose form:	Concentrate for solution for infusion
Strength:	350 mg/7 mL
Container:	Vial
Pack size:	One
Approved therapeutic use:	*Libtayo as monotherapy has provisional approval in Australia for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation.* *The decision to approve this indication has been made on the basis of objective response rate (ORR) and duration of response from single arm clinical studies. The sponsor is required to submit further clinical data to confirm the clinical benefit of the medicine*.
Route of administration:	Intravenous (IV) infusion
Dosage:	The recommended dose is 350 mg cemiplimab every 3 weeks (Q3W) administered as an IV infusion over 30 minutes.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

	Treatment may be continued until disease progression or unacceptable toxicity. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Sanofi-Aventis Australia Pty Ltd (the sponsor) to register Libtayo (cemiplimab) 350 mg concentrate for solution for infusion for the following proposed indication:

> *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.*

Cutaneous squamous cell carcinoma (CSCC) is a malignant proliferation of epidermal keratinocytes with invasion of the dermis and is distinguished from non-invasive precursor lesions such as actinic keratosis.[2] It is the second most common skin cancer affecting Caucasian populations worldwide, accounting for approximately 20% of all non-melanoma skin cancers.[3] Worldwide incidence varies widely, with the highest incidence in Australia and the lowest incidence in parts of Africa.[4]

The probability of cure from surgery is high for most CSCC patients; however, the disease course is life threatening for the small proportion of patients who develop metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC / laCSCC; herein collectively referred to as advanced CSCC). Most CSCC (70 to 80%) occurs on the sun exposed head and neck. Less than 5% of patients develop nodal metastases.[3]

There is no approved systemic treatment for advanced CSCC and there are no specific guidelines available for mCSCC or laCSCC. Available guidelines;[5] in Australia are outdated. Treatment guidelines for CSCC from the National Comprehensive Cancer Network (NCCN) in the US state that evidence regarding the effectiveness of systemic therapy is limited. The

[2] Fernandez Figueras M. From actinic keratosis to squamous cell carcinoma: pathophysiology revisited. *Journal of the European Academy of Dermatology and Venereology*. 2017;31:5-7.
[3] Goh A, et al. Managing patients with cutaneous squamous cell carcinoma metastatic to the axilla or groin lymph nodes. *Australasian Journal of Dermatology*. 2010;51(2):113-7.
[4] Lomas A, et al. A systematic review of worldwide incidence of nonmelanoma skin cancer. *British Journal of Dermatology*. 2012;166(5):1069-80.
[5] Network AC. Clinical Practice Guide Basal Cell Carcinoma, Squamous Cell Carcinoma (and Related Lesions)–A Guide to Clinical Management in Australia 2008.

NCCN recommends participation in clinical studies for CSCC patients but notes that these studies are scarce. Consensus-based interdisciplinary treatment guidelines from a European expert panel (with members from European Organisation for Research and Treatment of Cancer, European Association of Dermato-Oncology, and the European Dermatology Forum) state that there is no standard treatment regimen for CSCC.[6]

Known objective response rates / overall response rates (ORR) for other available treatments range widely across studies: 34 to 86% for chemotherapy;[7,8,9] 16% for gefitinib;[10]; 28% for cetuximab;[11] and 31% for panitumumab;[12]. Patients with very advanced disease should be provided with, or referred for, best supportive and palliative care to optimise symptom management and maximise quality of life.[13]

For most patients with CSCC, the recommended treatment is surgery/radiation therapy and is applied with a curative intent. However, for a small percentage of patients who develop mCSCC or laCSCC, the disease can be life threatening. Mono- or poly-chemotherapy is used in mCSCC noting that there are severe toxicities associated with platinum-based therapy. Targeted therapies, such as epidermal growth factor receptor (EGFR) inhibitors, either in combination with chemotherapy or in the neo-adjuvant setting, have shown some efficacy, although there is no established standard regimen and responses are usually short-lived. Use of commercially available treatments is limited by inconclusive efficacy data and substantial safety risks due to the generally advanced age of CSCC patients. Therefore, there is a significant unmet medical need for an effective treatment option for advanced CSCC that has an acceptable safety profile.

The below is extract from the United States (US) Food and Drug Administration (FDA) approved full prescribing information for Libtayo:[14]

> 'Binding of the programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2), to the programmed cell death protein 1 (PD-1) receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours.
>
> Cemiplimab-rwlc is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway mediated inhibition of the immune response, including the anti-tumour immune response. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.'

[6] Stratigos A, et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. *European journal of cancer*. 2015;51(14):1989-2007.
[7] Khansur T and Kennedy A. Cisplatin and 5-fluorouracil for advanced locoregional and metastatic squamous cell carcinoma of the skin. *Cancer*. 1991;67(8):2030-2.
[8] Sadek H, et al. Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. *Cancer*. 1990;66(8):1692-6.
[9] Shin DM, et al. Phase II study of induction chemotherapy with paclitaxel, ifosfamide, and carboplatin (TIC) for patients with locally advanced squamous cell carcinoma of the head and neck. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 2002;95(2):322-30.
[10] William Jr WN, et al. Gefitinib for patients with incurable cutaneous squamous cell carcinoma: a single-arm phase II clinical trial. Journal of the American Academy of Dermatology. 2017;77(6):1110-3. e2.
[11] Maubec E, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. *J Clin Oncol*. 2011;29(25):3419-26.
[12] Foote M, et al. Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma. *Annals of oncology*. 2014;25(10):2047-52.
[13] Alam M, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. Journal of the American Academy of Dermatology. 2018;78(3):560-78.
[14] FDA full prescribing information for Libtayo; (available from FDA website).

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been approved in United State of America (USA) (approved on 28 September 2018), Canada (approved on 10 April 2019) and European Union (EU) (approved on 28 June 2019), and was under consideration in Switzerland, Colombia and Israel.

Table 1: International regulatory status of Libtayo

Region	Submission date	Status	Approved indications
USA	28 February 2018	Approved on 28 September 2018	*Treatment of patients with metastatic cutaneous squamous cell carcinoma or locally advanced CSCC who are not candidates for curative surgery or curative radiation.*
EU	6 March 2018	Conditional approval on 28 June 2019	*Treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation.*
Canada	27 July 2018	Notice of compliance with conditions on 10 April 2019	*Treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation.* *Cemiplimab has been issued marketing authorisation with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorisation.*
Switzerland	3 July 2018	Under consideration	
Brazil	31 October 2018	Under consideration	
Colombia	13 February 2019	Under consideration	
Israel	01 April 2019	Under consideration	

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2019-03270-1-4

Description	Date
Designation (provisional)	16 July 2019
Submission dossier accepted and first round evaluation commenced	30 August 2019
First round evaluation completed	31 January 2020
Sponsor provides responses on questions raised in first round evaluation	2 March 2020
Second round evaluation completed	9 April 2020
Delegate's Overall benefit-risk assessment	19 June 2020
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	2 July 2020
Completion of administrative activities and registration on the ARTG	17 July 2020
Number of working days from submission dossier acceptance to registration decision*	195

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

The following publically available FDA documents were referenced by the Delegate.

- FDA review: New drug applications (NDA)/Biologics license applications (BLA) multi-disciplinary review and evaluation (BLA 761097) (Libtayo/cemiplimab).[15]
- FDA product label: FDA full prescribing information for Libtayo.[14]

The following publically available European Medicines Agency (EMA) documents were referenced by the Delegate.

- EMA review: Assessment report for Libtayo, EMA/CHMP/368468/2019.[16]
- EMA product information: Summary of product characteristics (SmPC) for Libtayo.[17]

[15] Information extracted from FDA:NDA/BLA multi-disciplinary review and evaluation for Libtayo. Available from FDA website.
[16] Information extracted from EMA European public assessment report (EPAR) for Libtayo. EMA/CHMP/368468/2019. 5 July 2019. Available from EMA website.

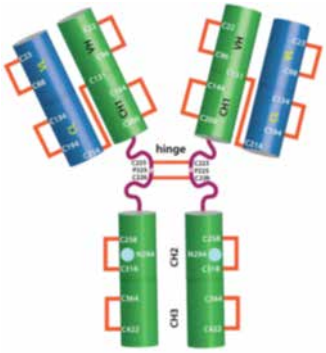
Quality

Cemiplimab is a recombinant fully-human IgG4 monoclonal anti-human PD-1 antibody (about 146kDa), produced by recombinant deoxyribonucleic acid (DNA) technology in Chinese hamster ovary (CHO) cell suspension culture. Cemiplimab binds specifically to PD-1 and blocks its interaction with ligands PD-L1 and PD-L2. Antagonising PD-L1 mediated inhibitory signalling in T cells, thereby rescuing the anti-tumour immune response.

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. Each heavy chain contains a serine to proline substitution at amino acid 225, (S228P, EU numbering, designated IgG4^{P}) within the hinge region of the Fc domain that reconstructs the human IgG1 hinge sequence (CPPC) to promote stabilization of disulfide bonds between the two heavy chains. There is a single N-linked glycosylation site (Asn^{294}) in each heavy chain, located within the CH2 domain of the fragment crystallisable region (Fc) constant region in the molecule. The antibody, based on the primary sequence (in the absence of N-linked glycosylation), has a molecular weight of 143,567.1 Da (chemical formula $C_{6380}H_{9808}N_{1688}O_{2000}S_{44}$), taking into account the formation of 16 disulfide bonds and removal of Lys^{444} from each heavy chain terminus. The complementarity determining regions (CDRs) within the heavy and light chain variable domains combine to form the binding sites of Cemiplimab to its target, PD-1.

The amino acid sequence of Cemiplimab is shown in Figure 1. A schematic representation of Cemiplimab, including the location of N-linked glycosylation sites and disulfide bond structures, is presented in Figure 2.

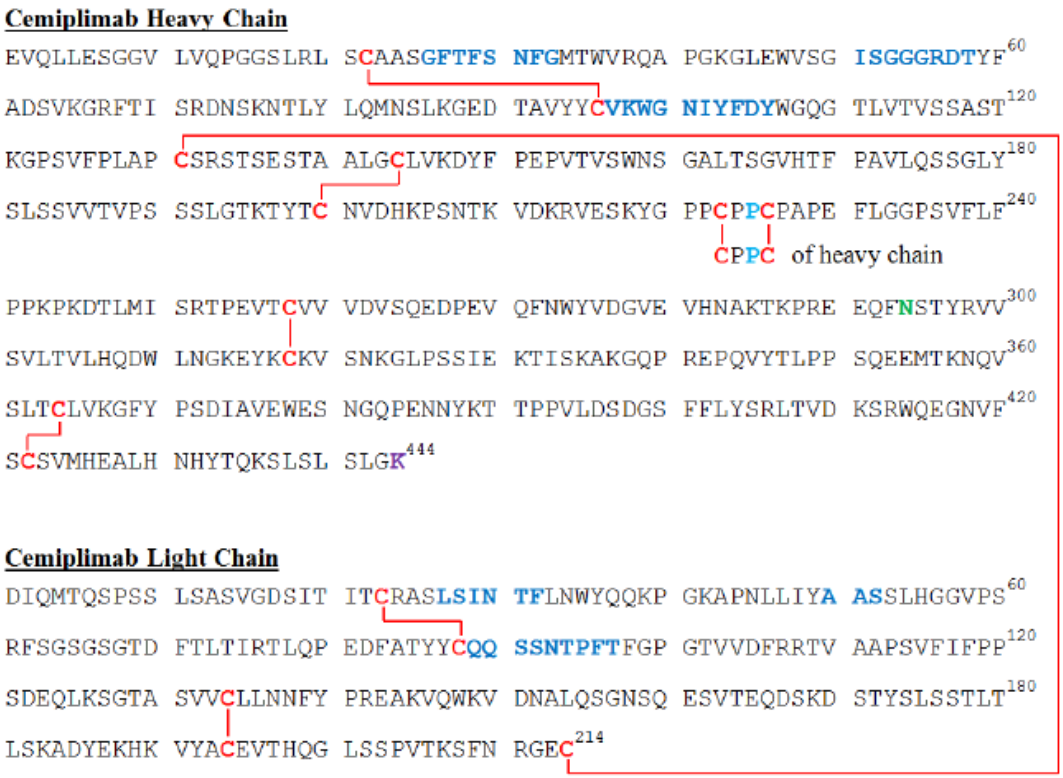
Figure 1: Schematic structural representation of cemiplimab



CH - constant region of the heavy chain, CL - constant region of the light chain. VH - variable region of the heavy chain, VL - variable region of the light chain. Orange - intra-chain and inter-chain disulfide bonds. Green and blue – Heavy and light chains, connected by inter-chain disulfide bonds.Cyan - Fc domain glycosylation site. Hinge region - heavy chain dimerisation by intermolecular disulfide bonds,# - hinge region substitution (Ser225 to Pro225) in each heavy chain

[17] Information extract from EMA Summary of Product Characteristics for Libtayo; revised 20 May 2020. Available from EMA website.

Figure 2: Primary amino acid sequence of cemiplimab



The sequences of the cemiplimab heavy chain and light chain CDRs are highlighted in blue. The cysteine residues (red) that have been confirmed to form the predicted disulfide bonds are connected by solid red lines. The Fc N-linked glycosylation site at Asn294 is highlighted in green. The heavy chain C-terminal Lys444 (purple) is predominantly removed during protein expression. Within the heavy chain hinge region, Ser225 (wild type IgG4) has been substituted to Pro225 (P in cyan) to promote stabilization of the cemiplimab IgG4 molecule. This substitution stabilizes the inter-chain disulfide bonds between the two heavy chains, and minimizes the potential for generating half-antibody.[18]

There are no objections to the approval of Libtayo (cemiplimab) 350 mg concentrate for solution for infusion provided all outstanding good manufacturing practice (GMP) clearances are obtained and remain current prior to decision.

Nonclinical

There are no objection to the provisional registration of cemiplimab from the nonclinical evaluator. Some amendments to the proposed PI were recommended.

The combined animal safety studies revealed the following findings of potential clinical relevance:

- autoimmune reactions
- adverse effects in the event of anti-drug antibody formation
- embryofetal lethality if used during pregnancy.

[18] Cemiplimab amino acids sequence extracted from KEGG DRUG Database (available at genome.jp)

Clinical

The clinical dossier includes:

- clinical study reports of the single arm studies, R2810-ONC-1540 (Study 1540) and R2810-ONC-1423 (Study 1423);
- study reports of population pharmacokinetics (R2810-MX-18022-SR-01V1) and exposure response analyses (R2810-PM-18032-CP-01V1);
- reports of integrated summary of efficacy and safety; and
- an expanded synopsis of the amendment (R2810-ONC-1540 Amendment 7) to incorporate an additional arm 6 to the 1540 pivotal study in order to provide additional data. This is part of the sponsor's commitment to the EU and is consistent with the requirements of the provisional registration pathway (a similar commitment to provide 'confirmatory' data is proposed for the TGA).

Clinical studies

R2810-ONC-1540 (Study 1540)

The main study supporting efficacy and safety of cemiplimab was R2810-ONC-1540 (Study 1540). It is a Phase II study of cemiplimab, a fully human monoclonal antibody to programmed cell death protein–1 (PD-1), in patients with advanced cutaneous squamous cell carcinoma (CSCC).

Study participants

The study included eligible patients with metastatic cutaneous squamous cell carcinoma (mCSCC) (nodal and/or distant) (Groups 1 and 3) and locally advanced cutaneous squamous cell carcinoma. (laCSCC) (Group 2). Group 3 (mCSCC) was opened for enrolment only after enrolment to Group 1 (mCSCC) was completed.

Key inclusion criteria

- histologically confirmed diagnosis of invasive CSCC;
- at least 1 lesion that was measurable by study criteria;
  - if a previously radiated lesion was to be followed as a target lesion, progression must have been confirmed by biopsy after radiation therapy. Previously radiated lesions may have been followed as non-target lesions if there was at least 1 other measurable target lesion;
    - Group 1 (mCSCC) and Group 3 (mCSCC): There had to be at least 1 baseline measurable lesion ≥ 10 mm in maximal diameter (1.5 cm for lymph nodes) according to RECIST;[19] version 1.1.
    - Group 2 (laCSCC): There must have been at least 1 measureable baseline lesion in which the longest diameter and the perpendicular diameter were both ≥ 10 mm if followed by digital medical photography. Non-measurable disease for Group 2 (laCSCC) was defined as either unidimensionally measurable lesions, tumours with margins that were not clearly defined, or lesions with maximum perpendicular diameters less than 10 mm.
- Eastern Cooperative Oncology Group (ECOG) performance status;[20] ≤ 1.

[19] RECIST: The Response Evaluation Criteria in Solid Tumors (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumor response using X-ray, CT and MRI.

Key exclusion criteria

- ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments
- prior treatment with an agent that blocks the PD-1/PD-L1 pathway
- brain metastases.

Treatments

Patients with CSCC received either:

- 3 mg/kg cemiplimab IV every 2 weeks (Q2W) in Group 1 (mCSCC) and Group 2 (laCSCC); or
- 350 mg cemiplimab IV every 3 weeks (Q3W) in Group 3 (mCSCC).

Duration of treatment: Group 3 (mCSCC) patients received 350 mg cemiplimab IV Q3W for up to 54 weeks (whereas patients in Group 1 (mCSCC) and Group 2 (laCSCC) received 3 mg/kg cemiplimab IV Q2W for up to 96 weeks).

Dose modification or interruption: toxicity management guidelines in the protocol indicated scenarios in which interruption or discontinuation of study treatment was required. Dose reduction of cemiplimab was allowed only in uncommon situations and only after discussion and agreement between the investigator and sponsor.

Primary objective

The primary objective of this study was to estimate the clinical benefit of cemiplimab monotherapy for patients with mCSCC treated Q2W (Group 1), laCSCC treated Q2W (Group 2), or mCSCC treated Q3W (Group 3), as measured by the ORR according to independent central review in each group.

Secondary objectives

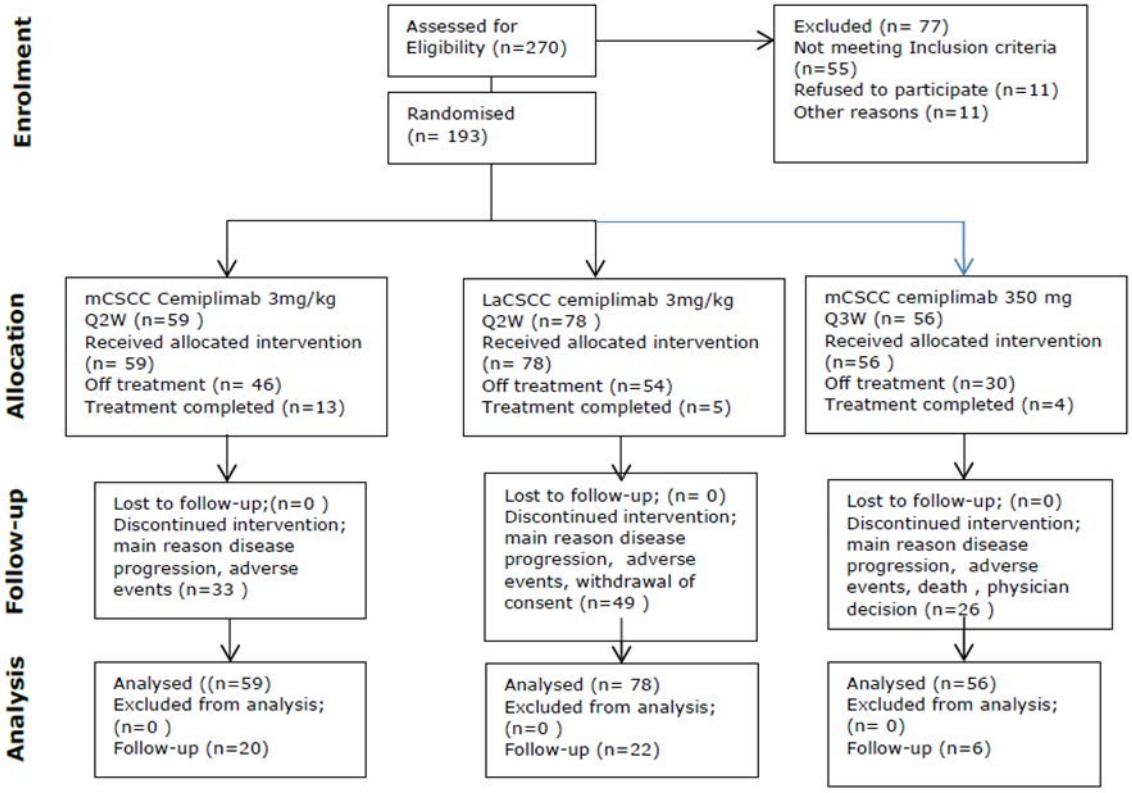
- to estimate the ORR according to investigator review
- to estimate the duration of response (DOR) and progression-free survival (PFS) by central and investigator review and overall survival (OS)
- to estimate the complete response (CR) rate by independent central review
- to assess the safety and tolerability of cemiplimab
- to assess the pharmacokinetics (PK) of cemiplimab (at select sites only)
- to assess the immunogenicity of cemiplimab.

Patient disposition

Patient disposition from Study 1540 is shown in the flow diagram below.

[20] ECOG performance status describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability. 0: Fully active, able to carry on all pre-disease performance without restriction. 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. 2: Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours. 3: Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours. 4: Completely disabled; cannot carry on any selfcare; totally confined to bed or chair. 5: Dead.

Figure 3: Study 1540 flow chart of patient disposition and study progress



Source: page 75 of the Libtayo EPAR.[16]

In the updated analysis, data cut off was 20 September 2018 for Group 1 and Group 3 patients and 10 October 2018 for Group 2 patients.

Efficacy

Results are available for 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%). Almost all recruited patients were white (98.3% in mCSCC and 100% in laCSCC group) and male (enrolment rate was 57% for females and 74% for males) which is in line with epidemiological data on CSCC.

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.

The efficacy results from Study 1540 are presented in Table 3.

Table 3: Study 1540 efficacy results, metastatic cutaneous squamous cell carinoma by dosing group and locally advanced cutaneous squamous cell carcinoma group

	mCSCC cemiplimab: 3 mg/kg Q2W (Group 1) (N = 59)	laCSCC cemiplimab: 3 mg/kg Q2W (Group 2) (N = 78)	mCSCC cemiplimab: 350 mg Q3W (Group 3) (N = 56)
	ICR	ICR	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.

Conclusion on efficacy

Study 1540 has shown a substantial ORR rate of 44% in patients with laCSCC and mCSCC treated with cemiplimab. DOR, the key secondary efficacy endpoint, is beyond 6 months for at least 93% of patients from Group 1 (there is more limited follow-up for Groups 2 and 3). The available data on the expression of PD-L1 suggest that this biomarker may lack predictive value to determine tumour responses in the proposed indication. The efficacy in terms of ORR is considered clinically relevant.

Safety

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 (Study 1423) and R2810-ONC-1540 (Study 1540).

Study 1423 was a Phase I, first-in-human, open-label, repeat dose study with cemiplimab as monotherapy and combination therapy. 397 adult patients (≥ 18 years old, males/females) with advanced solid malignancies in multiple cohorts were enrolled, among them 26 with CSCC. Expansion Cohort 7 evaluated cemiplimab 3 mg/kg Q2W monotherapy in 16 CSCC patients with distant metastatic disease (M1), and Expansion Cohort 8 evaluated cemiplimab 3 mg/kg Q2W monotherapy in 10 patients with locally and/or regionally advanced CSCC.

Immune-related adverse reactions (irAR) 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%). irARs led to permanent discontinuation of cemiplimab in 4.4% of patients.

The most common irARs were hypothyroidism (7.1%), pneumonitis (3.7%), skin adverse reactions (2.0%), hyperthyroidism (1.9%) and hepatitis (1.9%).

Adverse reactions were serious in 8.6% patients and led to permanent discontinuation of cemiplimab in 5.8% of patients.

Listed in Table 4 are adverse reactions by System Organ Class and by frequency.[17]

Table 5: 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 4 (continued): 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.

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.

Conclusion on safety

Considering the aging patient population and their exposure to prior treatments, the safety profile of cemiplimab corresponds to what can be expected from an anti-PD-1 antibody in Study 1540 and Study 1423.

The level of observed adverse events (AEs) and irARs are considered acceptable in the context of the disease being treated.

Risk management plan

The sponsor has submitted EU-RMP version 1.0 (26 April 2019; DLP 10 October) and ASA version 1.0 (31 July 2019) at the first round of evaluation and an updated ASA, version 1.1 (28 February 2020) at the second round of evaluation in support of this application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 5.[21]

Table 6: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Immune-related adverse reactions (irARs) (such as immune-related pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis, and other irARs)	ü*	ü†	ü	ü‡
	Infusion-related reactions (IRRs)	ü*	ü†	ü	ü‡
Important potential risks	Lack of effect due to anti-drug antibodies	ü	ü†	ü	–
Missing information	Long-term safety data	ü	ü†	–	–

*Includes specific adverse reaction follow up questionnaires; † Study R2810-ONC-1540; ‡ Patient guide and patient alert card

As Libtayo is being considered for a provisional registration it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> Libtayo (Cemiplimab) is to be included in the Black Triangle Scheme. The PI and Consumer Medicines Information (CMI) for Libtayo must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.

Risk-benefit analysis

Delegate's considerations

There is a high unmet medical need for patients with advanced CSCC as there are few systemic treatment options that have shown efficacy.

The clinical benefit observed for cemiplimab in this population is encouraging and is considered clinically meaningful in terms of ORR.

[21] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Therefore, the clinical benefit outweighs the toxicity and safety risks, which are considered manageable in the context of the disease being treated.

The submitted data support provisional registration of cemiplimab for the treatment of patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation.

See section 'proposed action' for the clinical study plan for provisional registration to generate further clinical data to confirm the clinical benefit of cemiplimab.

Proposed action

The Delegate proposes to include cemiplimab in the ARTG with the indication:

> *Libtayo as monotherapy has provisional approval in Australia 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.*
>
> *The decision to approve this indication has been made on the basis of ORR and DOR from single arm clinical studies. The sponsor is required to submit further clinical data to confirm the clinical benefit of the medicine.*

A condition of this provisional registration will be that the sponsor is required to submit further clinical data to confirm the clinical benefit of cemiplimab. See below for the clinical study plan extracted from sponsor submitted dossier.

The provisional registration application, comprises the same quality, nonclinical and clinical data (and their summaries) as was submitted in the EU, with a commitment for the provision of the same clinical data from ongoing studies in order to confirm the efficacy and safety of the drug. The specific obligation in the EU is outlined below and the same condition is proposed for Australia:

- In order to confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation, the marketing authorisation holder (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. (Due date: 31 Mar 2023).
  - The final study report for Groups 1 to 3 in the Phase II pivotal Study 1540. (Due date: 31 October 2022)

To confirm the results of cemiplimab in the treatment of advanced CSCC, Study 1540 is being amended to add another treatment arm (Group 6), which will enrol patients with advanced CSCC (n = 167) to receive 350 mg cemiplimab IV Q3W. The primary endpoint is ORR per independent central review. *REGN2810-ONC-1540 Amendment 7 Expanded Synopsis* in the clinical dossier provides rationale for Group 6, description of the patient population, schedule of events including baseline tumour biopsies, and the statistical plan.[22]

The on-going clinical study plan is outlined in Table 5 below and the protocols are included in sponsor submitted clinical dossier.

[22]Not included in this AusPAR.

Table 7: Clinical study plan for provisional registration

Study ID	Phase	Multiple arm (Y/N)	Randomised (Y/N)	Blinding (Y/N)	Co-administered therapy	Comparator	Proposed posology for provisional registration application	Study population	Study size total	Study size at determination (determination)	Duration	Primary endpoint	Confirmatory intent	Estimated submission
R2810-ONC-1540	II	Y	N	N	N	N	Cemiplimab administered IV over 30 minutes at: 3mg/kg Q2W or 350 mg Q3W	Adult patients with metastatic or locally advanced CSCC	137	137	Planned treatment duration was up to 96 weeks for Groups 1 and 2 and up to 54 weeks in Group 3	Objective Response Rate according to independent central review	To confirm the clinical efficacy and safety of cemiplimab monotherapy for patients with advanced CSCC	Interim report 31-Oct-2022
R2810-ONC-1540 (Group 6)	II	N	N	N	N	N	Cemiplimab 350 mg Q3W IV	Adult patients with metastatic or locally advanced CSCC	Approx 167	TBD	Patients will receive up to 108 weeks of treatment	Objective Response Rate according to independent central review	To confirm the clinical benefit of cemiplimab monotherapy for patients with advanced CSCC	Interim report 31-Mar-2023

Advisory Committee considerations[23]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA provisionally approved the registration of Libtayo cemiplimab 350 mg concentrate for solution for infusion, indicated for:

> *Libtayo as monotherapy has provisional approval in Australia for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation.*
>
> *The decision to approve this indication has been made on the basis of objective response rate (ORR) and duration of response from single arm clinical studies. The sponsor is required to submit further clinical data to confirm the clinical benefit of the medicine.*

[23] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific conditions of registration applying to these goods

- Libtayo (cemiplimab) is to be included in the Black Triangle Scheme. The PI and CMI for Libtayo must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.
- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided. Specifically the sponsor must conduct studies as described in the clinical study plan in version 1.1 (date 28 February 2020) of the Australia-Specific Annex. The following study report(s) should be submitted to TGA:
  - Study R2810-ONC-1540, by 31 October 2022
  - Study R2810-ONC-1540 (Group 6), by 31 March 2023

  Further guidance is available on the TGA website.
- The Libtayo EU-Risk Management Plan (RMP) (version 1.0, dated 26 April 2019, data lock point 10 October 2018), with Australian Specific Annex (version 1.1, dated 28 February 2020), included with submission PM-2019-03270-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- Batch release testing and compliance with Certified Product Details (CPD)
  - It is a condition of registration that all batches of Libtayo (cemiplimab) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the CPD.
  - It is a condition of registration that each batch of Libtayo (cemiplimab) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index.
  - The sponsor should be prepared to provide samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at http://www.tga.gov.au/publication/testing-biological-medicines. This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.
- Certified Product Details

The CPD, as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Libtayo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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