Australian Government

Department of Health

MSAC Application 1642

PD-L1 testing for access to Cemiplimab for the treatment of locally advanced or metastatic NSCLC

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): sanofi-aventis / Regeneron Pharmaceuticals
Corporation name: sanofi-aventis Australia Pty Ltd
ABN: 31 008 558 807
Business trading name: sanofi-aventis Australia Pty Ltd

Primary contact name: REDACTED

Primary contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

2. (a) Are you a lobbyist acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

☐ Yes
☐ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

PD-L1 testing for access to cemiplimab for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Lung cancer is the leading cause of cancer death in Australia and worldwide. At least 50% of lung cancer cases are stage III or IV at diagnosis (AIHW 2019a). The 5-year relative survival for stage III lung cancer is 17.1% and for stage IV only 3.2% (AIHW 2019 a,b).

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 85% of all lung cancer cases. The majority of NSCLC lack defined mutations (such as EGFR and ALK) that can be targeted by tyrosine kinase inhibitors.

NSCLC is most commonly treated with platinum-based chemoradiation and more recently immunotherapies, inhibiting programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1).

Australian Institute of Health and Welfare 2019a. Cancer in Australia 2019. Cancer series no.119. Cat. no. CAN 123. Canberra: AIHW.

AIHW 2019b. Cancer data in Australia. Web report Last updated: 26 Jul 2019. Available at: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/incidence-and-survival-by-stage Accessed 27/5/2020

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

The proposed service measures PD-L1 levels in tumour material from a patient diagnosed with NSCLC. A current MBS item determines if the requirements relating to PD-L1 status for access to pembrolizumab (a PD-1 inhibitor) under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. This submission requests an amendment of the item description to include cemiplimab, which is also a PD-1 inhibitor.

6. (a) Is this a request for MBS funding?

☒ Yes
☐ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

☒ Amendment to existing MBS item(s)
☐ New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

MBS item 72814, a Category 6 pathology service for:

Immunohistochemical examination by immunoperoxidase or other labelled antibody techniques using the programmed cell death ligand 1 (PD-L1) antibody of tumour material from a patient diagnosed with non-small cell lung cancer, to determine if the requirements relating to PD-L1 status for access to pembrolizumab under the Pharmaceutical Benefits Scheme are fulfilled.

Fee: $74.50 Benefit: 75% = $55.90 85% = $63.35.

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

i. ☐ An amendment to the way the service is clinically delivered under the existing item(s)
ii. ☐ An amendment to the patient population under the existing item(s)
iii. ☐ An amendment to the schedule fee of the existing item(s)
iv. ☐ An amendment to the time and complexity of an existing item(s)
v. ☐ Access to an existing item(s) by a different health practitioner group
vi. ☒ Minor amendments to the item descriptor that does not affect how the service is delivered
vii. ☐ An amendment to an existing specific single consultation item
viii. ☐ An amendment to an existing global consultation item(s)
ix. ☐ Other (please describe below):

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

i. ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☐ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☐ Yes
☒ No

(g) If yes, please advise:

Not applicable

7. What is the type of service:

☐ Therapeutic medical service
☒ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☐ Co-dependent technology
☐ Hybrid health technology

8. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

i. ☐ To be used as a screening tool in asymptomatic populations
ii. ☐ Assists in establishing a diagnosis in symptomatic patients
iii. ☐ Provides information about prognosis
iv. ☒ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
v. ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

☒ Pharmaceutical / Biological
☐ Prosthesis or device
☐ No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☐ Yes
☒ No

(b) If yes, please list the relevant PBS item code(s):

Not applicable

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

☐ Yes (please provide PBAC submission item number below)
☒ No

Application to the PBS expected to be made **REDACTED**

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Trade name: LIBTAYO
Generic name: Cemiplimab

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

☐ Yes
☒ No

(b) If yes, please provide the following information (where relevant):

Not applicable

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

No comment

(d) Are there any other sponsor(s) and/or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

No comment

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

No comment

12. Please identify any single and / or multi-use consumables delivered as part of the service?

No comment

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: *in-vitro* diagnostic test
Manufacturer's name: Dako
Sponsor's name: Agilent Technologies Australia Pty Ltd

The relevant cemiplimab clinical trial, R2810-ONC-1624 (Trial 1624; NCT03088540) used the same PD-1L test as pembrolizumab trials conducted by Merck, Sharp & Dohme, the Dako PD-L1 IHC 22C3 pharmDx test (Dako 22C3 test). The Dako 22C3 assay used to determine eligibility for enrolment in the KN-024 trial. This test was evaluated in prior submissions to MSAC:

- 1414 - PD-L1 testing for access to Pembrolizumab for the treatment of locally advanced or metastatic NSCLC
- 1440 - PD-L1 testing for access to pembrolizumab in treatment naïve patients with locally advanced or metastatic non-small cell lung cancer
- 1440.1 - PD-L1 testing for access to pembrolizumab in treatment naïve patients with locally advanced or metastatic non-small cell lung cancer.

The Public Summary Document for Application No. 1440.1 indicates that registration of the PD-L1 22C3 pharmDXTM kit was approved by the TGA on 17 November 2016. This kit is intended for use in the detection of PD-L1 protein in formalin-fixed paraffin-embedded (FFPE) NSCLC tissue using the Dako Autostainer Link 48 platform as an aid in identifying NSCLC patients for treatment with pembrolizumab. The SP263, SP142 and 28-8 antibody kits are also registered by the TGA.

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

☐ Class III
☐ AIMD
☒ N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

☒ Yes (if yes, please provide details below)
☐ No

Immunohistology cell marker IVDs
ARTG listing, registration or inclusion number: 282595 (Approved 17 November 2016)
Intended Purpose: For In-Vitro Diagnostic Use. IVDs that are intended to be used in histology and cytology to provide information about the presence and localisation of specific proteins and antigens present in histological tissue sections, cytological smears and fluids

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

Not applicable

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

☐ Yes (please provide details below)
☒ No

PART 4 – SUMMARY OF EVIDENCE

17. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*****
1.	Study R2810-ONC-1624 (Trial 1624), a Phase 3, open-label randomised controlled trial	NCT03088540. Study of REGN 2810 Compared to Platinum-Based Chemotherapies in Participants With Metastatic Non-Small Cell Lung Cancer (NSCLC). Press Releases from Sanofi and Regeneron of protocol-specified interim analysis	Patients with advanced NSCLC who tested positive for PD-L1 in ≥50% of tumour cells (N=712) were randomly assigned to cemiplimab 350mg intravenously every 3 weeks for up to 108 weeks, or a platinum-based, doublet chemotherapy regimen for 4-6 cycles. Patients in the chemotherapy arm were able to crossover to cemiplimab if their disease progressed.	https://clinicaltrials.gov/ct2/show/NCT03088540 https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-27-13-00-00 https://investor.regeneron.com/index.php/news-releases/news-release-details/phase-3-trial-libtayor-cemiplimab-monotherapy-first-line	NCT: First Posted: March 23, 2017. Last Update Posted: April 14, 2020. Press Release 27 April 2020

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
2.	KEYNOTE-024, a Phase 3, open-label randomised controlled trial	Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. Updated Analysis of KEYNOTE-024: Pembrolizumab versus platinum-based chemotherapy for advanced non–small-cell lung cancer with PD-L1 Tumor Proportion Score of 50% or greater. NCT02142738. Study of Pembrolizumab (MK-3475) Compared to Platinum-Based Chemotherapies in Participants With Metastatic Non-Small Cell Lung Cancer (MK-3475-024/KEYNOTE-024).	Patients with untreated advanced NSCLC with PD-L1 expression on ≥50% of tumour cells (N=305) were randomly assigned to pembrolizumab (200mg every 3 weeks) for 35 cycles or the investigator's choice of platinum-based chemotherapy for 4-6 cycles. Crossover from the chemotherapy group to the pembrolizumab group was permitted following disease progression.	Reck M, et al. 2016. N Engl J Med 2016;375:1823-33. DOI: 10.1056/NEJMoa1606774 Reck M, et al. 2019. J Clin Oncol 37:537-546. DOI: 10.1200/JCO.18.00149 https://clinicaltrials.gov/ct2/show/NCT02142738	Epub 2016 Oct 8. Epub 2019 Jan 8. *Follow-up to initial publication* Last Update Posted: December 24, 2019

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*
***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*
**** If the publication is a follow-up to an initial publication, please advise.*

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

None identified

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. **List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

    Clinical relevance was established for MSAC applications 1414, 1440, and 1440.1.

20. **List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

    No change from current criteria for MBS item 72814.

21. **List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

    No change from current criteria for MBS item 72814.

22. **List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

    MBS item 72814 is not specific to one brand of test.

23. **Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

    No change to proposed medical service and the current clinical management of the service from MSAC applications 1414, 1440, and 1440.1.

    REDACTED

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

Lung cancer is the leading cause of cancer death in Australia and worldwide. In Australia in 2019, there were an estimated 9,034 deaths due to lung cancer (5,179 males and 3,855 females), an age standardised rate (ASR) of 28.8 per 100,000 of the population and 18% of all cancer-related deaths (AIHW 2019a).

In Australia lung cancer is the fifth most common cancer diagnosed (excluding non-melanoma skin cancer). The estimated incidence of lung cancer in 2019 is 12,817 persons (7,184 males and 5,633 females), corresponding to an ASR of 41.2 per 100,000 persons (AIHW 2019a). Lung cancer is the third most commonly diagnosed cancer among people aged 65 years and older (9,517 cases in 2019).

The five-year prevalence at end of 2014 was 17,603 persons (9,411 males and 8,192 females).

In 2011, over 40% of lung cancer cases were stage IV at diagnosis and this may be an under-representation, as stage at diagnosis was not able to be derived for over a quarter of cases (AIHW 2019a).

The overall 5-year relative survival (2011–2015) for lung cancer is 17.8% (15.0% for males and 20.8% for females) but the 5-year survival for stage IV just 3.2%(AIHW 2019a,b).

Among Aboriginal and Torres Strait Islander people, lung cancer was the most common cancer diagnosed in the 5 years from 2010 to 2014 in New South Wales, Victoria, Queensland, Western Australia and the Northern Territory, and the most common cancer causing mortality, with a 5-year survival rate of just 10% (AIHW 2019a).

Mortality from lung cancer is also higher in very remote areas and socially disadvantaged areas (AIHW 2019a).

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for around 80-85% of cases.

The most common sub-types are:

- Adenocarcinoma - begin in mucus-producing cells in smaller airways and makes up about 40% of lung cancers. While this type of lung cancer is most commonly diagnosed in current or former smokers, it is also the most common lung cancer in non-smokers.
- Squamous cell (epidermoid) carcinoma - commonly develops in the cells that line the larger airways of the lung (bronchi). Approximately 30% of lung cancers.
- Large cell undifferentiated carcinoma - can appear in any part of the lung and are not clearly squamous cell or adenocarcinoma (large round cells under the microscope).

Staging of NSCLC is as follows:

- Stage 1 - The tumour is in only one lobe of the lung and has not spread.
- Stage 2 - The tumour has spread to nearby lymph nodes, or has grown into the chest wall.
- Stage 3A - Tumours have spread to lymph nodes in the centre of the chest (mediastinum).
- Stage 3B - Tumours have spread more extensively to lymph nodes in the mediastinum, or have become attached to major blood vessels or the trachea (windpipe).
- Stage 4 - The cancer cells have spread to distant parts of the body, such as the bones, brain or liver.

Australian Institute of Health and Welfare 2019a. Cancer in Australia 2019. Cancer series no.119. Cat. no. CAN 123. Canberra: AIHW.

AIHW 2019b. Cancer data in Australia. Web report Last updated: 26 Jul 2019. Available at: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/incidence-and-survival-by-stage Accessed 27/5/2020

25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

NSCLC affects mainly the elderly and is often diagnosed at stage IV (

Figure ***1***).

Symptoms of lung cancer may include (Cancer Council Australia 2019):

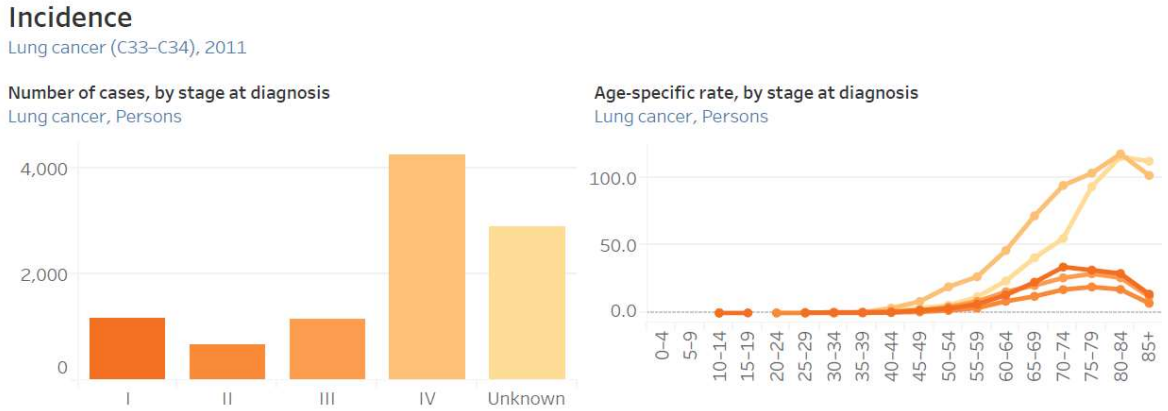
- shortness of breath and wheezing
- hoarseness
- chest pain
- coughing or spitting up blood
- a new cough that does not go away
- recurring bronchitis or pneumonia
- loss of appetite
- unexplained weight loss
- fatigue.

Factors that can increase the risk of lung cancer include (Cancer Council Australia 2019):

- smoking tobacco or exposure to second-hand smoke
- exposure to asbestos or radon; exposure to occupational substances such as uranium, chromium, nickel, diesel fumes and soot
- HIV infection
- family history
- history of lung diseases such as lung fibrosis or emphysema.

The burden of lung cancer is higher among Aboriginal and Torres Strait Islander people, very remote areas and socially disadvantaged areas (AIHW 2019a).

Figure 1: Incidence of lung cancer by stage and age



Source: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/incidence-and-survival-by-stage

Australian Institute of Health and Welfare 2019a. Cancer in Australia 2019. Cancer series no.119. Cat. no. CAN 123. Canberra: AIHW.

Cancer Council. 2019. Lung Cancer. Available at: cancer.org.au/about-cancer/types-of-cancer/lung-cancer.html Accessed 24/06/2020. Page last updated on: Friday, March 22, 2019.

26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

Diagnosis of lung cancer may include a number of tests as follows (Cancer Council 2019).

- Chest X-ray, which can show larger tumours (more than 1cm wide).
- A computerised tomography (CT) scan uses X-ray beams to take pictures inside your body and create a cross-sectional image. A CT scan is able to detect smaller tumours as well as providing information about the tumour and lymph nodes.
- A positron emission tomography (PET) scan is used to stage lung cancer after a diagnosis.
- A lung function test (spirometry)
- Biopsy - a small sample of tissue will be taken if a tumour is suspected after a CT scan or X-ray. There are different types of biopsy including a bronchoscopy, CT-guided core biopsy and endobronchial ultrasound.
- Sputum cytology

All patients suspected of having NSCLC, based on CT scan or X-ray, will undergo a biopsy at initial diagnosis to determine histology, including the sub-type of NSCLC. The biopsy can be used for genetic testing (EGFR, ALK) and PD-L1 expression by IHC.

PART 6b – INFORMATION ABOUT THE INTERVENTION

27. Describe the key components and clinical steps involved in delivering the proposed medical service:

Patients suspected of having NSCLC based on CT scan or X-ray will undergo a biopsy at initial diagnosis to determine histology. For patients with NSCLC of squamous histology, assessment of PD-L1 status through immunohistochemistry (IHC) will be the only biomarker test undertaken at diagnosis. For patients who have non-squamous or not otherwise specified NSCLC, PD-L1 IHC testing will be performed at initial diagnosis, along with EGFR and ALK testing.

The pembrolizumab PSD (1440.1) indicates that PD-L1 testing is to be performed on tissue sections taken from a biopsy specimen obtained as part of standard diagnostic work-up. IHC (for PD-L1 testing) only uses one 4-5 micron section compared to approximately 50 microns required for EGFR mutation testing, and so it is unlikely that a re-biopsy would be required for the PD-L1 test alone. The addition of the PD-L1 biomarker to the testing protocol at initial diagnosis would be unlikely to increase the overall re-biopsy rate. A re-biopsy may be required due to PD-L1 expression changes in patients diagnosed at an earlier stage disease and receiving subsequent treatment. However, cytology samples (fine needle aspirations and effusions) may be used for PD-L1 testing.

28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

The relevant cemiplimab clinical study (Trial 1624) was conducted using the same PD-L1 test as for pembrolizumab (manufactured by Dako).

The pembrolizumab PSD (1440.1) indicates that this test is the PD-L1 22C3 pharmDX^{TM} kit approved by the TGA on 17 November 2016. The kit is intended for use in the detection of PD-L1 protein in formalin-fixed paraffin-embedded (FFPE) NSCLC tissue using the Dako Autostainer Link 48 platform as an aid in identifying NSCLC patients for treatment with pembrolizumab.

Other test kits, the SP263, SP142 and 28-8 antibody kits are also registered by the TGA. The MBS item descriptor does not specify which test must be used.

29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

No change to MBS item 72814

30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

No

31. If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:

No

32. If applicable, advise which health professionals will primarily deliver the proposed service:

No change to MBS item 72814

33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

No change to MBS item 72814

34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

No change to MBS item 72814

35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

If applicable, insert advice regarding training or qualifications

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select <u>ALL</u> relevant settings):

- ☐ Inpatient private hospital (admitted patient)
- ☐ Inpatient public hospital (admitted patient)
- ☐ Private outpatient clinic
- ☐ Public outpatient clinic
- ☐ Emergency Department
- ☐ Private consulting rooms - GP
- ☐ Private consulting rooms – specialist
- ☐ Private consulting rooms – other health practitioner (nurse or allied health)
- ☐ Private day surgery clinic (admitted patient)
- ☐ Private day surgery clinic (non-admitted patient)
- ☐ Public day surgery clinic (admitted patient)
- ☐ Public day surgery clinic (non-admitted patient)
- ☐ Residential aged care facility
- ☐ Patient's home
- ☒ Laboratory
- ☐ Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

Not applicable

37. Is the proposed medical service intended to be entirely rendered in Australia?

- ☒ Yes
- ☐ No

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

This is a minor change to the existing MBS item 72814 to allow treatment with cemiplimab or pembrolizumab instead of pembrolizumab only, should cemiplimab be listed on the PBS for patients with NSCLC.

39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

☒ Yes (please list all relevant MBS item numbers below)
☐ No

MBS item 72814.

40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):

Patients are considered for treatment with pembrolizumab.

41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

☐ In addition to (i.e. it is an add-on service)
☒ Instead of (i.e. it is a replacement or alternative)

(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

Uptake will be established for the PBAC submission via expert opinion or market research but can be estimated as approximately **REDACTED** uptake is expected for two reasons:

1. The clinical evidence supporting proposed TGA registration and PBS listing, Trial 1624, was designed to enrol patients with untreated advanced NSCLC with PD-L1 expression on ≥50% of tumour cells, whereas the current TGA indication and PBS listing for pembrolizumab is untreated advanced NSCLC with PD-L1 expression on ≥1% of tumour cells.

2. Pembrolizumab has been PBS listed for untreated advanced NSCLC since November 2018.

42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):

Patients are considered for treatment with pembrolizumab or cemiplimab, rather than pembrolizumab only.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

The submission to the PBAC will claim equivalent health outcomes in efficacy and safety for cemiplimab versus pembrolizumab based on similarly designed clinical trials. The medical service is for the same group of patients (advanced NSCLC).

Result of screening test

The final pembrolizumab PSD (1440.1) indicates that "the median prevalence of PD-L1 TPS ≥50% for both Australia and the broader Caucasian population prevalence is 26% (range 22–29) and 29% (range 25–30), respectively. These values are consistent with the proposed prevalence of 28.5% for the base case in the pembrolizumab economic evaluation".

Effectiveness

For patients who are found to have advanced NSCLC with PD-L1 expression on ≥50% of tumour cells, similar outcomes can be expected with cemiplimab versus pembrolizumab.

The evidence for cemiplimab is based on study R2810-ONC-1624 (Trial 1624; NCT03088540). Trial 1624 was an open-label, randomised, multicentre trial that compared the effects of cemiplimab monotherapy to platinum doublet chemotherapy in 712 patients with advanced NSCLC who tested positive for PD-L1 in ≥50% of tumour cells. Patients were randomised to receive either cemiplimab 350 mg intravenously every 3 weeks for up to 108 weeks, or a platinum-based, doublet chemotherapy regimen for 4 to 6 cycles.

A protocol-specified interim analysis was reported by Sanofi and Regeneron 27 April 2020[1]. Although one-third of the patients had enrolled within the past 6 months, the primary endpoint of OS was met. Compared with platinum doublet chemotherapy, treatment with cemiplimab reduced the risk of death by 32.4% (HR 0.676; 95% CI, 0.525-0.870; P=0.002).

The key relevant trials for comparison with pembrolizumab are KEYNOTE-024 (NCT02142738) and the subgroup with PD-1 tumour proportion score (TPS) ≥ 50% in KEYNOTE-042 (NCT02220894).

KEYNOTE-024 was an open-label, Phase 3 trial, in which 305 patients who had previously untreated advanced NSCLC with PD-L1 expression on ≥ 50% of tumour cells and no sensitising mutation of the EGFR gene or translocation of the ALK gene were randomly assigned to receive either pembrolizumab (at a fixed dose of 200 mg every 3 weeks) for 35 cycles or the investigator's choice of platinum-based chemotherapy for 4 to 6 cycles. Crossover from the chemotherapy group to the pembrolizumab group was permitted in the event of disease progression.

At the second interim analysis with a median duration of follow-up of 11.2 months (range, 6.3 to 19.7), the HR for death was 0.60 (95% CI, 0.41 to 0.89); (P=0.005) (Reck et al. 2016).

At the final protocol-specified OS analysis with a median duration of follow-up of 25.2 months (range, 20.4 to 33.7 months), the median OS was 30.0 months (95% CI, 18.3 months to NR) in the pembrolizumab arm and 14.2 months (95% CI, 9.8 to 19.0 months) in the chemotherapy arm (HR, 0.63; 95% CI, 0.47 to 0.86; one-sided nominal P=0.002) (Reck et al. 2019).

KEYNOTE-042 was also an open-label, Phase 3 randomised trial of pembrolizumab versus platinum-doublet chemotherapy, but did not permit crossover to pembrolizumab for patients in the chemotherapy arm and allowed for enrolment of patients with PD-L1 TPS ≥1% (Mok et al. 2019). The study was designed to evaluate OS in three cut-points of PD-L1 TPS sequentially, starting with PD-L1 TPS ≥50%, then PD-L1 TPS ≥20%, and then PD-L1 TPS ≥1%.

There were 1274 total randomised patients, 599 (47%) with PD-L1 TPS ≥50%. OS was improved with pembrolizumab compared with chemotherapy at each cut point [HR for OS: TPS ≥50%, 0.69 (95% CI 0.56–

[1] https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-27-13-00-00 and https://investor.regeneron.com/index.php/news-releases/news-release-details/phase-3-trial-libtayor-cemiplimab-monotherapy-first-line

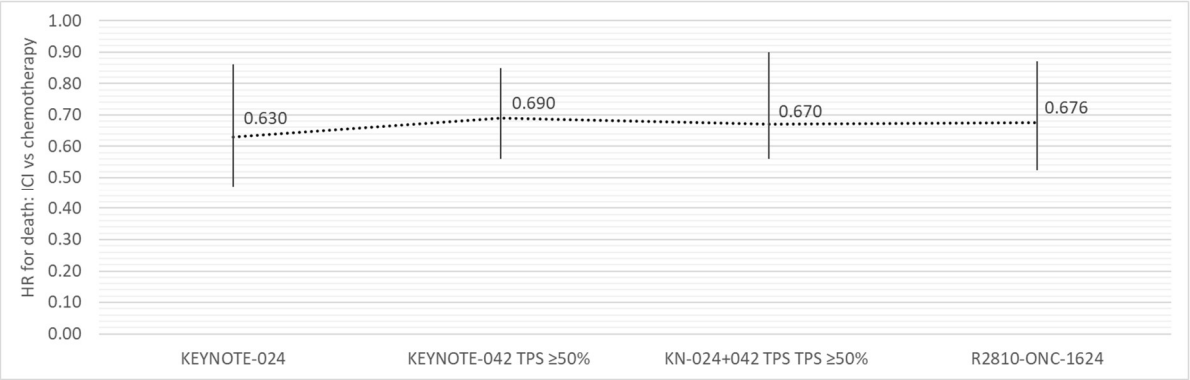
0.85), P=0.0003; TPS ≥20%, 0.77 (95% CI 0.64–0.92), P=0.0020; TPS ≥1%, 0.81 (95% CI 0.71–0.93), P=0.0018].

The survival benefit was largely driven by the PD-L1 TPS ≥50% cohort. Among patients with PD-L1 TPS 1%–49%, improvement in OS with pembrolizumab was not observed [HR 0.92 (95% CI 0.77–1.11)] and the response rate was 16.6% for pembrolizumab and 21.7% for chemotherapy (Peters et al. 2019).

In a combined analysis of KEYNOTE-024 and the PD-L1 TPS ≥50% cohort of KEYNOTE-042, the HR for OS is 0.67 (95% CI: 0.56, 0.90) (PBAC March 2019).

Comparison of the data for overall survival in first line trials for NSCLC with PD-1 ≥50% is shown in Figure 2. A visual inspection of the currently available data for OS (HR for death with 95% CI) suggests that the data are similar. For the PBAC submission, further comparison of the trials and analysis of statistical non-inferiority criteria will be completed.

Figure 2: Comparison of hazard ratio for death for immune checkpoint inhibitors pembrolizumab (KEYNOTE trials) and cemiplimab (Trial 1624) vs, platinum-based chemotherapy



Safety

The pembrolizumab MSAC submission nominated current practice, i.e. no test and treatment with platinum-based doublet chemotherapy for all patients, as the main comparator. This is unchanged from the previous submission. In relation to comparative safety, the PSD for MSAC Application No. 1440.1 summarises the following.

As PD-L1 testing is to be performed on tissue sections taken from a biopsy specimen obtained as part of standard diagnostic work-up, it would not incur any direct risks to patients. IHC only uses one 4-5 micron section compared to approximately 50 microns required for EGFR mutation testing, and so it is unlikely that a re-biopsy would be required for the PD-L1 test alone. The addition of the PD-L1 biomarker to the testing protocol at initial diagnosis would be unlikely to increase the overall re-biopsy rate.

A re-biopsy may be required due to PD-L1 expression changes in patients diagnosed at an earlier stage disease and receiving subsequent treatment. The main risk to the patient would then be complications such as pneumothorax and haemorrhage. However, the critique noted that if cytology samples (fine needle aspirations and effusions) were used for PD-L1 testing, the associated risks would be reduced.

Mok TSK et al. 2019. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. The Lancet 393(10183):1819-1830.

PBAC March 2019. PEMBROLIZUMAB, Powder for injection 50 mg, solution concentrate for I.V. infusion 100 mg in 4 mL, Keytruda®. Published 5 July 2019. Available at: https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2019-03/pembrolizumab-psd-march-2019

Peters S, et al. 2019. How to make the best use of immunotherapy as first-line treatment of advanced/metastatic non-small-cell lung cancer. Annals of Oncology 30: 884–896. doi:10.1093/annonc/mdz109

Reck M, et al. 2016. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33. DOI: 10.1056/NEJMoa1606774.

Reck M, et al. 2019. Updated Analysis of KEYNOTE-024: Pembrolizumab versus platinum-based chemotherapy for advanced non–small-cell lung cancer with PD-L1 Tumor Proportion Score of 50% or greater. J Clin Oncol 37:537-546.

44. Please advise if the overall clinical claim is for:

☐ Superiority
☒ Non-inferiority

45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes: There are no changes to the safety outcomes of the test **Clinical Effectiveness Outcomes:** There are no changes to the clinical effectiveness outcomes of the test

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. Estimate the prevalence and/or incidence of the proposed population:

The requested PBS listing for cemiplimab for the treatment of NSCLC will be made on the basis of a cost minimisation to pembrolizumab and therefore a market share approach will be used for the estimated utilisation. Likewise, the addition of cemiplimab to MBS item 72814 will not increase the total utilisation of this service. A proportion of patients tested under MBS item 72814 will be considered for cemiplimab instead of pembrolizumab PBS treatment.

47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

Once-off test at diagnosis to determine treatment options.

48. How many years would the proposed medical service(s) be required for the patient?

Once-off test at diagnosis to determine treatment options.

49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

The requested listing is a cost-minimisation to current service 72814. Last calendar year there were 3,161 services for this item and a proportion of patients tested under MBS item 72814 will be considered for cemiplimab instead of pembrolizumab PBS treatment.

50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

A proportion of services for item 72814 will be used for cemiplimab instead of pembrolizumab. If the uptake is **REDACTED**, this would be **REDACTED** services. There is no risk of leakage as the requested use is unchanged and the requested PBS listing will also be aligned with pembrolizumab's.

PART 8 – COST INFORMATION

51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

Not applicable, cost minimisation to current service (72814).

The Public Summary Document for MSAC application 1440.1 states: *"MSAC advised that the appropriate fee for the test should be $74.50, in line with MBS item 72848 (IHC of one, two or three of the oestrogen, progesterone or HER2 antibodies). MSAC considered the higher fee was justified because the test requires counting of cells and assessment of staining intensity".*

52. Specify how long the proposed medical service typically takes to perform:

Not applicable, cost minimisation to current service (72814)

53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Category 6 – PATHOLOGY SERVICES
72814 Proposed item descriptor: Immunohistochemical examination by immunoperoxidase or other labelled antibody techniques using the programmed cell death ligand 1 (PD-L1) antibody of tumour material from a patient diagnosed with non-small cell lung cancer, to determine if the requirements relating to PD-L1 status for access to pembrolizumab or cemiplimab under the Pharmaceutical Benefits Scheme are fulfilled. Fee: $74.50 Benefit: 75% = $55.90 85% = $63.35