Australian Government

Department of Health

Application Form

(New and Amended Requests for Public Funding)

(Version 2.5)

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 in order 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.

The application form will be disseminated to professional bodies / organisations and consumer organisations that have will be identified in Part 5, and any additional groups that the Department deem should be consulted with. The application form, with relevant material can be redacted if requested by the Applicant.

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

Phone: +61 2 6289 7550

Fax: +61 2 6289 5540

Email: hta@health.gov.au

Website: MSAC Website

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):
Corporation name: Merck Sharp & Dohme (Australia) Pty Limited
ABN: **redacted**
Business trading name: **redacted**

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 consultant acting on behalf of an Applicant?

☐ Yes

☒ No

(b) If yes, what is the Applicant(s) name that you are acting on behalf of?

Insert relevant Applicant(s) name here.

3. (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

4. Application title

PD-L1 (Programmed Death 1 Ligand) IHC (immunohistochemistry) testing for access to pembrolizumab as first-line therapy for patients with unresectable or metastatic bladder cancer ineligible for cisplatin-based therapy.

5. 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)

Stage IV advanced/metastatic bladder cancer. Patients with stage IV bladder cancer have cancer that has extended through the bladder wall and invaded the pelvic and/or abdominal wall and/or has lymph node involvement and/or spread to distant sites. Stage IV bladder cancer is also referred to as "unresectable or metastatic" bladder cancer.

6. 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)

It is proposed that immunohistochemistry (IHC) test for evaluation of Programmed Cell Death- Ligand 1 (PD-L1) expression to determine eligibility for treatment with pembrolizumab, be undertaken in patients diagnosed with unresectable or metastatic bladder cancer. The tissue removed as part of a standard biopsy will be used for immunohistochemical testing with PD-L1. The testing would be done by a pathologist alongside other immunohistochemical tests which are done routinely, and it would be proposed that the test is a pathologist determinable test.

7. (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:

MSD has made previous applications to support a co-dependent technology submission for access to pembrolizumab in PD-L1 positive non-small cell lung cancer patients (Application 1414 and 1440) as well as access to pembrolizumab in PD-L1 positive metastatic bladder cancer where patients have recurred or progressed following platinum-based chemotherapy (Application 1445)

(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):

Insert description of 'other' amendment here

(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:

Insert description of other public funding mechanism here

8. 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

9. 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
vi. ☐ Is for genetic testing for heritable mutations in clinically affected individuals and, when also appropriate, in family members of those individuals who test positive for one or more relevant mutations (and thus for which the Clinical Utility Card proforma might apply)

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

☒ Pharmaceutical / Biological

☐ Prosthesis or device

☐ No

11. (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):

Keytruda (pembrolizumab) is currently PBS listed for use in metastatic melanoma (10424P, 10436G, 10475H, 10493G)

(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

This application is being lodged to support a co-dependent technology submission for access to pembrolizumab in patients with unresctable or metastatic bladder cancer who express PD-L1. Keytruda is also PBS listed for use in metastatic melanoma (10424P, 10436G, 10475H, 10493G)

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

Trade name: KEYTRUDA

Generic name: Pembrolizumab

12. (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):

Billing code(s): Insert billing code(s) here

Trade name of prostheses: Insert trade name here

Clinical name of prostheses: Insert clinical name here

Other device components delivered as part of the service: Insert description of device components here

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

☐ Yes

☐ No

(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?

☐ Yes

☐ No

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

Insert sponsor and/or manufacturer name(s) here

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

Single use consumables: The PD-L1 test comes as part of a kit (PD-L1 IHC 22C3 pharmDx™ Assay). The kit is designed for 50 single use tests.

Multi-use consumables: Insert description of multi use consumables here

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. (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: The PD-L1 test is a Class III in vitro diagnostic test which uses IHC. (GMDN code: CT1056 Immunohistology cell marker IVDs)

Manufacturer's name: Dako Pty Limited

Sponsor's name: Merck Sharp & Dohme (Australia) Pty Limited

(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

15. (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

ARTG listing, registration or inclusion number: Insert ARTG number here

TGA approved indication(s), if applicable: Insert approved indication(s) here

TGA approved purpose(s), if applicable: Insert approved purpose(s) here

16. 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?

☐ Yes (please provide details below)
☒ No

Date of submission to TGA: Insert date of submission here

Estimated date by which TGA approval can be expected: Insert estimated date here

TGA Application ID: Insert TGA Application ID here

TGA approved indication(s), if applicable: If applicable, insert description of TGA approved indication(s) here

TGA approved purpose(s), if applicable: If applicable, insert description of TGA approved purpose(s) here

17. 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

Estimated date of submission to TGA: March 2016

Proposed indication(s), if applicable:

The PD-L1 IHC 22C3 pharmDx™ Assay

(developed by Dako)is a qualitative assay intended for use in the detection of PD-L1 in formalin-fixed, paraffin embedded (FFPE) non small cell lung carcinoma (NSCLC) tissue samples using the Dako Automated Link 48 Platform. The PD-L1 IHC 22C3 pharmDx™ Assay is indicated as an aid in identifying NSCLC patients for treatment with a PD-1 inhibitor. It is expected that a similar indication, with some variation, will be used for the bladder indication

Proposed purpose(s), if applicable:

To identify patients for access to pembrolizumab for the treatment of unresectable or metastatic bladder cancer who express PD-L1.

PART 4 – SUMMARY OF EVIDENCE

18. **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.	non-randomised trial	Phase 2 study of pembrolizumab (MK-3475) as first-line therapy for patients with unresectable or metastatic urothelial cancer ineligible for cisplatin-based therapy (KEYNOTE-052)	KEYNOTE-052 is a phase 2 study of pembrolizumab as first-line therapy for adults with unresectable or metastatic urothelial cancer who are ineligible for cisplatin. All patients must provide a biopsy sample for PD-L1 evaluation. Primary endpoint is ORR. Up to 350 patients will be enrolled. KEYNOTE-052 is currently enrolling patients (ClinicalTrials.gov, NCT02335424)	Link to article	Poster at 2015 ASCO Annual Meeting
2.	non-randomised trial	Pembrolizumab (Pembro; MK-3475) for advanced urothelial cancer: Results of a phase IB study Pembrolizumab (MK-3475) for advanced urothelial cancer: Updated results and biomarker analysis from KEYNOTE-012 (KEYNOTE-012)	KEYNOTE-012 is a phase 1b study investigating safety, tolerability and anti-tumor activity of pembrolizumab in participants with advanced solid tumours (breast, head/neck, urothelial, and gastric cancer). A total of 297 patients were planned for recruitment. Among the 33 patients enrolled with advanced urothelial cancer, 52% received 2 prior therapies. The study is ongoing (ClinicalTrials.gov, NCT01848834)	link to article link to article	Poster at 2015 Genitourinary Cancers Symposium Oral presentation at 2015 ASCO Annual Meeting

** 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.*

19. 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.*

Not applicable

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

20. 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):

- Medical Oncology Group of Australia
- Royal College of Pathologists of Australasia

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

Not applicable

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

To be confirmed

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

Not applicable

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

Name of expert 1: **redacted**

Telephone number(s): **redacted**

Email address: **redacted**

Justification of expertise: **redacted**

Name of expert 2: **redacted**

Telephone number(s): **redacted**

Email address: **redacted redacted**

Justification of expertise: **redacted**

Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

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

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

25. 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:

Bladder cancer is found in the cells of the bladder lining where the most common risk factors include smoking, older age, being male and chemical exposure at work. These are called transitional cells, so the condition is known as 'transitional cell bladder cancer'. There are two main types of transitional cell cancers are: Non-invasive bladder cancer and invasive bladder cancer where the cancer has spread into the muscle layer of the bladder or further. The main treatments for non-invasive bladder cancer are surgery, intravesical chemotherapy and immunotherapy (Bacillus Calmette-Guérin known as BCG). In most cases, surgery, alone or combined with other treatments is used. Non-invasive bladder cancer should be treated aggressively with early intervention and strict follow-up as there may be a tendency to progress to an invasive malignancy.

When the bladder cancer has invaded the muscle or beyond (metastatic), the most common treatment is surgery by cystectomy (removal of the bladder) and if required in combination with systemic chemotherapy and/or radiotherapy. Patients with metastatic bladder cancer present a challenge at this stage of the disease as a variety of chemotherapeutic agents used in this setting provide a generally poor prognosis.

Bladder cancer is the 10th most commonly diagnosed cancer in Australia, with approximately 2,800 patients diagnosed each year and accounting for 1,140 deaths in 2015[1]. Bladder cancer accounts for approximately 2% of all new cancers in Australia and is one of only a few cancers in Australia in which overall survival has declined over the last thirty years. The five-year overall survival rate has fallen from 67 to 53 per cent between 1982 and 2011[2].

26. 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:

It is proposed that PD-L1 testing be undertaken in patients diagnosed with unresectable or metastatic bladder cancer. Of those diagnosed in Australia, the incidence of bladder cancer is more than three times higher in men than in women where the mean age is approximately 75 years.

Per standard diagnostic workup, the patient would undergo a biopsy. The tissue removed as part of the biopsy and used for the unresectable or metastatic bladder cancer diagnosis confirmation would be used for immunohistochemical testing with PD-L1. The testing would be done by a pathologist alongside other immunohistochemical tests which are done routinely, and it would be proposed that the test is a pathologist determinable test.

The test would be undertaken prior to commencement of pembrolizumab to enable identification of those patients most likely to benefit from treatment.

[1] Cancer in Australia: an overview 2014, AIHW, Table B4(a), Pg 92 of document, AIHW Cancer in Australia an overview [accessed 7th April 2016]

[2] Cancer in Australia: an overview 2014, AIHW, Five-year relative survival; Change over time Pg 38 of document, AIHW Cancer in Australia an overview [accessed 10th April 2016]

27. 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):

Patients diagnosed with unresectable or metastatic bladder cancer are treated with gemcitabine + cisplatin in the first line setting. Approximately 1 in 2 patients with unresctable or metastatic bladder cancer are ineligible for cisplatin, mainly due to renal dysfunction and/or poor performance status. In this situation, these patients are treated with a combination with a combination of carboplatin + gemcitabine or either carboplatin or gemcitabine monotherapy. However these therapies are generally associated with a poor prognosis, and new, more effective treatments are needed.

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

Pembrolizumab is a highly selective humanised monoclonal antibody that targets the PD-L1 receptor to potentiate an immune response. PD-L1 expression in bladder cancer tumour biopsies can be assessed using immunohistochemical (IHC) testing with antibodies that bind specifically to the PD-L1 protein.

The PD-L1 assay that will be used during the pembrolizumab bladder cancer clinical development program is known as the PD-L1 IHC 22C3 pharmDx™ Assay (developed by Dako). This assay will be used to assess PD-L1 expression in bladder cancer tumour biopsies in the KEYNOTE 052 (KN052) clinical study. Patients are enrolled into the KN052 study irrespective of PD-L1 tumour status, i.e. all comers. The PD-L1 IHC 22C3 pharmDx™ Assay

will be used to determine PD-L1 expression in tumour tissue in order to explore the relationship between tumour PD-L1 expression and response to treatment with pembrolizumab.

Detailed information of the PD-L1 IHC 22C3 pharmDx™ Assay kit components as well as its performance studies will be presented for MSAC consideration in the co-dependent technology submission.

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

There are currently no PD-L1 tests reimbursed by MSAC. The PD-L1 IHC 22C3 pharmDx™ Assay will be made commercially available in Australia. TGA registration of the PD-L1 IHC 22C3 pharmDx™ Assay , including any applicable registered trademark, is being undertaken by Dako. Registration is pending but is scheduled to be completed prior to consideration of the co-dependent technology submission by MSAC.

30. 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?

Insert description of approach here

31. 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):

Accessibility

Currently there are no commercially available diagnostic kits for testing of PD-L1 expression levels. Thus, PD-L1 testing is not currently being carried out on patients in Australia, apart from testing in the clinical trial or research setting. However, in the management of bladder cancer, the taking of biopsy specimens is currently part of standard practice and diagnostic work-up. Testing for PD-L1 expression should be carried out at time of diagnosis, concurrent with differentiation of histologic subtypes.

Frequency

As per the protocols for the KN012 and KN052 studies, only one PD-L1 test was required through the course of their disease. The test would be undertaken prior to commencement of pembrolizumab to enable identification of those patients most likely to benefit from treatment.

Sample consideration

There is currently no known role for PD-L1 testing in monitoring a patient's response to pembrolizumab treatment. As mentioned previously, KN-052 will include patients enrolled on the basis of archival or newly obtained biopsy tissue. This information will be used to help inform the type of sample required for PD-L1 expression testing. MSD will present this information for MSAC's consideration as part of a co-dependent technology submission. In addition, the application will seek to provide information on other relevant sample considerations as needed. These could include information on:

- Biopsy location
- Type of tissue (e.g. archival or newly obtained)
- Impact of prior exposure to treatment (e.g. radiation or chemotherapy)

32. 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:

As IHC testing is a common procedure and as PD-L1 expression is anticipated to be frequently identified (64.2% of cases for ≥1% PD-L1 expression: Plimack et al. 2015), it is proposed that PD-L1 IHC testing be eligible to be carried out in any pathology laboratory holding the appropriate accreditation to claim pathology services through the MBS. In practice, it is anticipated that the majority of PD-L1 testing would occur in pathology laboratories associated with a public hospital.

A certified pathologist would be responsible for conducting the test and reporting the results. Consistent with introduction of diagnostic tests associated with access to other targeted therapies, pathologist training and quality assurance programs would be expected to be developed with respect to delivery of diagnostic tests for access to treatments targeting the PD-1 pathway on the PBS.

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

N/A

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

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

A certified pathologist would be responsible for conducting the test and reporting the results. Specialists including urologists or oncologists may provide a referral for PD-L1 testing.

36. 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:

Consistent with introduction of diagnostic tests associated with access to other targeted therapies, pathologist training and quality assurance programs would be expected to be developed with respect to delivery of diagnostic tests for access to treatments targeting the PD-1 pathway on the PBS.

37. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select all relevant settings):

- ☐ Inpatient private hospital
- ☐ Inpatient public hospital
- ☐ Outpatient clinic
- ☐ Emergency Department
- ☐ Consulting rooms
- ☐ Day surgery centre
- ☐ Residential aged care facility

☐ Patient's home

☒ Laboratory

☐ Other – please specify below

It is anticipated that the majority of PD-L1 testing would occur in pathology laboratories associated with a public hospital.

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

N/A

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

☒ Yes

☐ No – please specify below

Specify further details here

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

39. 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):

The comparator is no PD- L1 testing and current standard of care (Gemcitabine+Carboplatin or Gemcitabine/Carboplatin monotherapy)

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

☐ Yes (please provide all relevant MBS item numbers below)

☒ No

N/A as the comparator is no PD-L1 testing and current standard of care as per Q.38.

41. Define and summarise the current clinical management pathways 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 diagnosed with unresctable or metastatic bladder cancer are treated with gemcitabine + cisplatin in the first line setting. Approximately 1 in 2 patients with unrectable or metastatic bladder cancer are ineligible for cisplatin, mainly due to renal dysfunction and/or poor performance status. In this situation, these patients are treated with a combination with a combination of carboplatin + gemcitabine or either carboplatin or gemcitabine monotherapy (see attachment).

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

☒ Yes

☐ No

(b) If yes, please outline the extent of which the current service/comparator is expected to be substituted:

There are currently no PD-L1 tests reimbursed by MSAC and therefore the proposed test will replace standard of care.

43. 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 diagnosed with unresectable or metastatic bladder cancer will receive PD-L1 testing. Patients eligible for cisplatin will still receive gemcitabine + cisplatin in the first line setting. Patients ineligible for cisplatin who are PD-L1 positive will receive pembrolizumab. Patients ineligible for cisplatin who are PD-L1 negative will be treated with a combination of carboplatin + gemcitabine or either carboplatin or gemcitabine monotherapy (see attachment).

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

44. 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):

PD-L1 testing followed by treatment with pembrolizumab is associated with superior outcomes compared to no testing and current standard of care for patients with unresectable or metastatic bladder cancer ineligible for cisplatin-based therapy.

Hence, the clinical claim is driven by two factors:

1. Acceptable safety and analytical performance of PD-L1 test. (To be assessed by MSAC.)
2. Superior effectiveness with acceptable safety of treating PD-L1 positive patients with pembrolizumab relative to standard of care without testing. (To be assessed by PBAC).

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

☒ Superiority

☐ Non-inferiority

46. 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:

- Psychological and physical harms from testing.
- Any adverse events related to a change in treatment including tolerability; toxicity (particularly immune-related adverse events).

Clinical Effectiveness Outcomes:

- Primary outcomes: Overall survival; quality of life; progression free survival
- Secondary outcomes: response rate (complete response or partial response according to RECIST and irRC criteria); disease control rate (response rate + rate of stable disease); duration of response; rate of disease progression; time to progression.

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

Incidence

Estimated no. of patients diagnosed with bladder cancer (includes all stages) (2016)[1]: 2,880

Eligible patient pool for PD-L1 testing in the first year following MSAC listing

Estimated no. of patients living with bladder cancer (includes all stages) (2016)	2,880[1]
Percentage of cases diagnosed with unresectable or metastatic bladder cancer	38%[2,3]
Bladder cancer patients ineligible for cisplatin	50%[4,5]
Eligible patient pool for PD-L1 testing	Approximately 550

[1]Cancer in Australia: an overview 2014, AIHW, Table B4(a) Pg 92 of document[accessed 8 Jul 2016]

[2]http://blcwebcafe.org/content/view/137/148/lang,english/

[3]NIHR Horizon Scanning Research & Intelligence Centre

[4]Galsky 2011

[5] Data derived from Clinician input

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

Per the KN012 and KN052 protocols, only one PD-L1 test was required through the course of disease. The test would be undertaken prior to commencement of pembrolizumab to enable identification of those patients most likely to benefit from treatment. There is currently no known role for PD-L1 testing in monitoring a patient's response to pembrolizumab treatment.

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

It is presumed that only one PD-L1 test is required per patient through the course of disease.

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

As presented in Item 46, the estimated patients who will utilise the PD-L1 test is approximately 550 for the first year (2016). Since the PD-L1 test is a one-off test which will only be performed when the patient is diagnosed with unresectable or metastatic bladder cancer, the estimated number of patients who will be tested in the forthcoming years will only include those incident patients who are newly diagnosed with unresectable or metastatic bladder cancer.

51. 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:

Currently, patients with unresectable or metastatic bladder cancer who are ineligible for cisplatin are treated with non-cisplatin chemotherapies including carboplatin or gemcitabine. If the KN052 results indicate that PD-L1 positive patients are most likely to benefit from pembrolizumab therapy, pembrolizumab could replace non-cisplatin chemotherapies as standard of care in PD-L1 positive patients. Consequently the uptake of PD-L1 test would be 100% for all patients diagnosed with unresectable or metastatic bladder cancer.

It is presumed that only patients with tumour expression of PD-L1 are eligible for pembrolizumab. Therefore uptake of pembrolizumab is likely restricted to those who have a PD-L1 expression in tumour tissues. It is assumed that 20% patients are PD-L1 positive. The risk of leakage for PD-L1 testing is minimal as testing would be restricted to those patients potentially eligible for pembrolizumab.

PART 8 – COST INFORMATION

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

The final fee request will be contingent on decisions made by DAKO, the company who will be commercialising the test. The expected fee for the proposed service is consistent with other immunohistochemical tests.

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

The IHC service testing for PD-L1 expression can take between 2.5-4 hours depending on instrumentation and protocol used.

54. 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 (insert proposed category number here) – (insert proposed category description here)
Proposed item descriptor: Immunohistochemical examination of biopsy material by immunoperoxidase or other labelled antibody techniques using the PD-L1 antibody to determine if the requirements relating to programmed cell death ligand 1 (PD-L1) status for access pembrolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $ (to be determined)

PART 9 – FEEDBACK

The Department is interested in your feedback.

55. How long did it take to complete the Application Form?

Insert approximate duration here

56. (a) Was the Application Form clear and easy to complete?

☐ Yes

☐ No

(b) If no, provide areas of concern:

Describe areas of concern here

57. (a) Are the associated Guidelines to the Application Form useful?

☐ Yes

☐ No

(b) If no, what areas did you find not to be useful?

Insert feedback here

58. (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?

☐ Yes

☐ No

(b) If yes, please advise:

Insert feedback here