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: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): N/A
Corporation name: Roche Products Pty Limited
ABN: 70 000 132 865
Business trading name: Roche Products

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 Ligand 1) immunohistochemistry (IHC) testing for access to atezolizumab as first-line therapy for patients with locally advanced or metastatic triple-negative breast cancer (TNBC).

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)

Breast cancer is the most frequently diagnosed cancer among women and is the leading cause of cancer-related deaths in women word-wide (1, 2). Triple-negative breast cancer, a distinct subtype of breast cancer with the worst prognosis, is characterised immunohistologically by the lack of expression of hormonal estrogen receptor (ER) and progesterone receptor (PgR) and lack of overexpression and/or amplification of the human epidermal growth factor 2 (HER2)/NEU gene (3).

Triple-negative breast cancer accounts for between 12-20% of newly diagnosed breast cancer cases and approximately 15-20% of breast cancer cases overall (4, 5). Compared to other breast cancer subtypes, TNBC tumours are generally larger in size, more poorly differentiated, have more extensive lymph-node involvement at diagnosis, and exhibit an invasive phenotype. Patients with TNBC have a higher risk of both local and distant recurrence, and metastases are more likely to occur in visceral organs and the brain rather than bone compared to patients with other breast cancers (6).

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)

The proposed medical service is an IHC test for evaluation of PD-L1 expression to determine eligibility for treatment with atezolizumab in patients with locally advanced or metastatic TNBC who are previously untreated in the advanced setting. The biopsy sample taken as part of a standard diagnostic process 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.

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:

(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

No other source of funding for PD-L1 testing other than the MBS is sought, however in this co-dependent submission public funding for PBS-access to atezolizumab is also being sought.

(g) If yes, please advise: Not applicable

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):

An application seeking PBS listing of atezolizumab for the treatment of locally advanced or metastatic TNBC is planned to be lodged for consideration by the PBAC as part of this co-dependent submission.

(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

An integrated co-dependent submission to MSAC/PBAC is proposed for PD-L1 testing to determine PBS access to atezolizumab.

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

Trade name: TECENTRIQ®
Generic name: atezolizumab

12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List? Not applicable

☐ Yes
☐ No

(b) If yes, please provide the following information (where relevant): Not applicable

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)? Not applicable

☐ 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? Not applicable

☐ Yes
☐ No

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s): Not applicable

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

Single use consumables: PD-L1 is evaluated using the PD-L1 OptiView Amplification Kit that is used in conjunction with the OptiView Detection Kit on a VENTANA BenchMark ULTRA instrument. PD-L1 may also be evaluated using alternate kits and instrumentation platforms (e.g. PD-L1 IHC 28-8 pharmDx kit and Dako Autostainer Link 48 platform).
Multi-use consumables: Not applicable

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: PD-L1 inhibitor, atezolizumab, Tecentriq®
Manufacturer's name: Roche Products Pty Ltd
Sponsor's name: Roche Products Pty Ltd

Type of therapeutic good: PD-L1 in vitro diagnostic test VENTANA PD-L1 (SP142) Assay
Manufacturer's name: Roche Diagnostics Pty Ltd
Sponsor's name: Roche Diagnostics Pty Ltd

A comparison to alternative commercial PD-L1 test kits for TNBC will be presented for MSAC consideration in the co-dependent technology submission.

(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)?

Tecentriq

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

ARTG listing, registration or inclusion number: AUST R 277120

TGA approved indication(s), if applicable:
Non-small cell lung cancer
Tecentriq is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, Tecentriq should be used after progression on or after targeted therapy.

Tecentriq is not currently TGA-approved for patients with TNBC; however, is in the process of being considered by the TGA (see Q16 below).

SP142 Assay

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

TGA approved purpose(s), if applicable: The diagnostic test has yet to be included on the ARTG as a class III IVD with companion diagnostic claims.

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?

Tecentriq

☒ Yes (please provide details below)
☐ No

Date of submission to TGA for mTNBC: Redacted
Estimated date by which TGA approval can be expected: Redacted
TGA Application ID: PM-2018-04446-1-4
TGA approved indication(s), if applicable: First-line, locally advanced or metastatic TNBC
TGA approved purpose(s), if applicable: N/A

SP142 Assay

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

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?

SP142 Assay

☒ Yes (please provide details below)
☐ No

Estimated date of submission to TGA: Redacted
Proposed indication(s), if applicable: Locally advanced or metastatic TNBC
Proposed purpose(s), if applicable: PD-L1 testing to determine PBS-access to atezolizumab

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	Open-label Phase 1 trial	Long-term clinical outcomes and biomarker analyses of atezolizumab therapy for patients with metastatic triple-negative breast cancer	Women with metastatic TNBC were enrolled in a multi-cohort open-label, phase 1 study at US and European academic medical centres. Eligible patients regardless of line of therapy had measurable disease by RECIST, version 1.1; ECOG PS of 0-1; and a representative tumour sample for assessment of immune cell (IC) PD-L1 expression	https://jamanetwork.com/journals/jamaoncology/fullarticle/2701722	13 September 2018
2	Randomised Phase 3 trial	A Phase 3, multicentre, randomised, placebo-controlled study of atezolizumab in combination with nab-paclitaxel compared with placebo with nab-paclitaxel for participants with previously untreated metastatic triple-negative breast cancer (IMpassion130)	IMpassion130 is a multicentre, randomised, double-blind study evaluating the efficacy, safety and pharmacokinetics of atezolizumab administered with nab-paclitaxel compared with placebo in combination with nab-paclitaxel in participants with locally advanced or metastatic TNBC who have not received prior systemic therapy for metastatic breast cancer. This study is currently active, but not recruiting. Primary Outcome Measures: Progression free survival (PFS) in ITT population PFS in PD-L1 expressers Overall survival (OS) in ITT population OS in PD-L1 expressers	https://www.nejm.org/doi/pdf/10.1056/NEJMoa1809615	20 October 2018

** 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.*

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1	Randomised Phase 3 trial	A Phase 3, multicentre, randomised, double-blind, placebo-controlled study of atezolizumab and paclitaxel versus placebo and paclitaxel in participants with previously untreated locally advanced or metastatic triple-negative breast cancer (IMpassion131)	IMpassion131 is a multicentre, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of atezolizumab administered in combination with paclitaxel in participants with previously untreated, inoperable locally advanced or metastatic, centrally confirmed TNBC. This study is currently recruiting. Primary Outcome Measure: Progression free survival (PFS) in ITT population	ClinicalTrials.gov Identifier: NCT03125902	February 2019 (Estimated primary completion date)
2	Randomised Phase 3 trial	A Phase 3, randomised, double-blind, placebo-controlled, multicentre study of the efficacy and safety of atezolizumab plus chemotherapy for patients with early relapsing recurrent triple-negative breast cancer (IMpassion132)	IMpassion132 is a study designed to evaluate the efficacy and safety of atezolizumab plus chemotherapy compared with placebo plus chemotherapy in patients with inoperable recurrent triple-negative breast cancer. This study is currently recruiting. Primary Outcome Measure: Overall survival (OS) in ITT population	ClinicalTrials.gov Identifier: NCT03371017	July 2019 (Estimated primary completion date)

** 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.*
****Date of when results will be made available (to the best of your knowledge).*

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):

The Royal College of Pathologists of Australasia (RCPA). Roche have approached RCPA and have yet to receive a response. Roche recommends that the Department approach them directly.

Medical Oncology Group of Australia (MOGA). A letter of clinical relevance has been sent to the Department independent of this application.

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

MOGA and RCPA.

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

The Breast Cancer Network of Australia (BCNA).

BCNA is the peak national organisation for Australians affected by breast cancer, and consists of a network of more than 120,000 members and 288 Member Groups. More than 90 per cent of members have had a diagnosis of breast cancer. BCNA works to ensure that Australians affected by breast cancer receive the very best support, information, treatment and care appropriate to their individual needs.

A letter of support from BCNA is attached to this application.

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

There are currently no PD-L1 tests listed on the MBS for patients with TNBC. However, MSAC/PBAC recently recommended a new MBS item for the ICH testing of PD-L1 expression to help determine eligibility for PBS-subsidised pembrolizumab in patients with locally advanced or metastatic NSCLC. Both therapeutic goods were listed on respective schemes on 1 November 2018.

In addition to the Roche/Ventana SP142 PD-L1 assay, there are a number of tests commercially available in Australia. The main assays are:

MSD/Dako PD-L1 22C3 pharmDx assay;

Roche/Ventana SP263 PD-L1 IHC assay.

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: Internationally recognised Professor in the field of molecular pathology in cancer. Redacted sits on many pharmaceutical advisory boards for breast, lung and some gastrointestinal tumours. Redacted has research collaborations both nationally and internationally on novel markers and pathways implicated in particular areas of tumour development.

Name of expert 2: Redacted

Telephone number(s): Redacted

Email address: Redacted

Justification of expertise: Redacted internationally recognised breast cancer specialist. Redacted was on the global independent steering committee redacted on the IMpassion130 clinical trial.

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:

Breast cancer is the most frequently diagnosed cancer among women and is the leading cause of cancer-related deaths in women worldwide. In 2012, almost 1.7 million new breast cancer cases were diagnosed (25% of all cancers in women) and 521,900 deaths were estimated to have occurred (1, 2).

Triple-negative breast cancer, a distinct phenotype of breast cancer with the worst prognosis, is characterised immunohistologically by the lack of expression of hormonal receptors ER and PgR and lack of overexpression and/or amplification of the human epidermal growth factor receptor 2 (HER2)/NEU gene (3). Triple-negative breast cancer accounts for between 12-20% of newly diagnosed breast cancer cases (4, 5). Patients with metastatic TNBC typically have relatively poorer outcomes (higher frequency of progression, shorter duration of PFS and worse OS) compared with other breast cancer subtypes (7, 8).

Despite optimal use of the best currently available systemic therapy, virtually all women with advanced TNBC will ultimately die from their disease (9). As of 2014, the 5-year survival for advanced TNBC is estimated at 9% (based on the most recent estimates from the Surveillance, Epidemiology, and End Results (10). Cytotoxic chemotherapy remains the mainstay of treatment for both early-stage and advanced TNBC.

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:

Determination of breast cancer molecular subtype provides valuable prognostic information and determines which treatment path a patient will follow. Given this, it is a standard part of the workup of breast cancer diagnosis. In general, the expression of three receptors on the tumour are routinely determined in clinical practice: ER, PgR, HER2.

It is proposed that the test for PD-L1 expression in patients with locally advanced or metastatic TNBC would be ordered by the treating physician when treatment with atezolizumab is being considered. In patients diagnosed with de novo locally advanced or metastatic TNBC, this would be carried out using the tissue samples taken as part of the standard diagnostic work-up (see above). The tissue removed as part of the biopsy and used for the advanced breast cancer diagnosis confirmation would then also be used for IHC testing for PD-L1 expression. The testing would be done by a pathologist alongside other IHC tests which are performed routinely and the pathologist would be responsible for conducting the test and interpreting results. In patients diagnosed with early stage TNBC and who subsequently develop metastases, a re-biopsy may be necessary.

The proposed PBS-restriction for atezolizumab will be for first-line treatment of locally advanced or metastatic TNBC. The application to PBAC for PBS listing of atezolizumab will include clinical data in all-comer patients and in patients expressing PD-L1. This application to MSAC requests consideration of PD-L1 testing in order to access atezolizumab as a contingency for the scenario in which the PBAC recommends PBS listing of atezolizumab in PD-L1 positive patients only. The testing would enable identification of those patients most likely to benefit from treatment with atezolizumab.

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):

Triple negative breast cancer patients remain the patient group with the largest unmet need within advanced metastatic breast cancer. Anthracyclines and/or taxane and/or platinum-based chemotherapy is recommended as initial treatment. The choice of regimen depends on patient characteristics, previous treatment in the early breast cancer setting and clinician choice.

The current and proposed clinical treatment algorithms are provided as an attachment to this application form.

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

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

The VENTANA SP142 IHC assay was used to assess PD-L1 expression in the IMpassion130 clinical trial. Patients were enrolled in the IMpassion130 trial, irrespective of PD-L1 tumour status, i.e. all comers. The relationship between tumour PD-L1 expression and response to treatment with atezolizumab was also explored.

Detailed information on the SP142 IHC 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?

On the 1 November 2018, a new MBS item was listed for the IHC testing of PD-L1 expression to help determine eligibility for PBS-subsidised pembrolizumab in patients diagnosed with NSCLC. The MBS item descriptor does not nominate the use of a specific trademarked assay. Similarly, it is not anticipated that a specific trademarked assay would be required to perform PD-L1 IHC testing in TNBC patients.

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?

N/A

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

All patients with locally advanced or metastatic TNBC will have a biopsy taken as part of a standard diagnostic work-up. It is proposed that PD-L1 expression testing be carried out on the tissue sample when treatment with atezolizumab is being considered.

Frequency

As per the IMpassion130 study protocol, only one PD-L1 test was required throughout the course of a patient's disease to determine eligibility for treatment. The test would be undertaken prior to commencement of atezolizumab to enable identification of patients most likely to benefit from treatment. There is no known role of the PD-L1 test in monitoring a patient's response to treatment.

Sample consideration

The IMpassion130 trial utilised PD-L1 testing on both archival and newly obtained biopsy samples. This information will be used to help inform the type of sample required for PD-L1 testing. Roche will present this information for MSAC's consideration as part of a co-dependent technology submission. Further relevant sample considerations such as biopsy location will also be presented.

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:

Immunohistochemistry testing is a well-established technique in all major pathology laboratories. Laboratories already have the platform infrastructure and reagents to perform PD-L1 IHC testing. The PD-L1 antibody is the only additional resource required.

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

A certified pathologist would be responsible for conducting the testing and reporting of results.

As discussed, IHC is a well-established technique and a common procedure. It is proposed that PD-L1 testing be eligible to be carried out in any pathology laboratory holding the appropriate accreditation to claim pathology services through the MBS.

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

It is not anticipated that any other professional, other than a certified pathologist would be able to conduct IHC testing for PD-L1 expression.

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 involved in the diagnosis and care of patients with TNBC, including oncologists may provide a referral for PD-L1 IHC 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:

It is expected that, consistent with the introduction of other IHC diagnostic tests for other targeted therapies, that pathologist training and a quality assurance program would be developed. This would address interpretation of the test results for PD-L1 positivity specific to the SP142 assay and for other assays/antibodies that are likely to be available. There is currently a pathologist training and quality assurance program underway for PD-L1 testing for NSCLC.

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

Specify further details here

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each: Not applicable

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

☒ Yes
☐ No – please specify below

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. As described previously, patients with locally advanced or metastatic TNBC are treated with anthracycline and/or taxane and/or platinum-based therapy in the first-line setting. There is no recommendation for one specific chemotherapy. The choice of regimen depends on patient characteristics, previous treatment in the early breast cancer setting and clinician choice.

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

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):

The nominated comparator is 'no test' and to treat with standard of care. As discussed previously, patients with locally advanced or metastatic TNBC are treated with anthracycline and/or taxane and/or platinum-based therapy in the first-line setting. The choice of regimen depends on patient characteristics, previous treatment in the early breast cancer setting and clinician choice.

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

☒ Yes
☐ No

The proposed medical service (PD-L1 testing) will be used instead of the comparator (no PD-L1 testing).

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

There are currently no publically funded PD-L1 tests available in Australia for patients with TNBC. Therefore, all patients with locally advanced or metastatic TNBC would require the PD-L1 test to be performed prior to accessing atezolizumab.

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):

In current practice, PD-L1 testing is not required to access treatment for patients with TNBC. Patients with locally advanced or metastatic TNBC are currently treated with anthracycline and/or taxane and/or platinum-based therapy, depending on patient factors, previous treatment in the early breast cancer setting and clinician choice.

Through the introduction of the proposed PD-L1 test, patients who are deemed to be PD-L1 positive will be able to access atezolizumab.

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):

It is proposed that PD-L1 testing followed by atezolizumab-based treatment is superior to no testing and current standard of care for patients with locally advanced or metastatic TNBC who are PD-L1 positive. The clinical claim is justified by:

1. Acceptable safety and analytical performance of the PD-L1 test (as assessed by MSAC)
2. Superior efficacy with acceptable safety of atezolizumab-based treatment in PD-L1 positive patients relative to standard of care (without PD-L1 testing) (as assessed by PBAC)
3. Clinical utility of the test plus drug combination (as assessed be MSAC/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 or toxicity, particularly from immune-related adverse events.

Clinical Effectiveness Outcomes:

Test Outcomes:

Trial based (evidentiary standard) PD-L1 assay analytical performance:

Sensitivity

Specificity

Positive predictive value

Negative predictive value

Comparative performance of PD-L1 testing methods:

Concordance with other commercially available PD-L1 assays

Re-testing rates

Drug Outcomes:

Progression free survival (PFS) (according to RECIST)

Response rate and duration of response

Overall Survival (OS)

Health-related quality of life

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

It is proposed that patients would be tested for PD-L1 expression when the clinician has determined the patient may benefit from treatment with atezolizumab and have therefore met the PBS criteria to access treatment. The proposed PBS criteria for atezolizumab is for patients with locally advanced or metastatic TNBC who have not received prior chemotherapy for their advanced disease.

Based on current information to date, the best estimate of the population to be tested is based on assumptions presented in Table 1 below. The estimated incidence is based on the Australia Institute of Health and Welfare (AIHW) projected figures for 2018.

Please note that the co-dependent MSAC/PBAC submission will include further detailed information to supplement these estimates.

Table 1 Estimated eligible population in 2018

Projected new cases of breast cancer (2018) (11)	18235
Proportion metastatic (12)	15%
Proportion mTNBC (12)	17%
Population size eligible for testing	465

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

As discussed previously, there is no known role for testing PD-L1 expression to monitor response to atezolizumab therapy. As such, PD-L1 testing will be performed only once to determine patient eligibility to receive treatment with atezolizumab.

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

It is proposed that the PD-L1 test will be required only once per patient.

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

As per Q 47 above, it is estimated that approximately 465 patients would utilise the PD-L1 test in the first year. This assumes an 100% test rate.

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:

The clinical claim is that PD-L1 testing and treatment with atezolizumab is superior to current standard of care. Given this, atezolizumab-based treatment could replace current standard of care in PD-L1 positive locally advanced or metastatic TNBC patients. It is estimated that the uptake of PD-L1 testing would be 100% for all patients diagnosed with locally advanced or metastatic TNBC. By 2020, it is estimated that approximately 492 patients would utilise the PD-L1 test. The risk of leakage would be negligible as testing would be restricted to those patients who are potentially eligible to receive atezolizumab as requested. A detailed utilisation analysis will be presented in the co-dependent MSAC/PBAC submission.

PART 8 – COST INFORMATION

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

MSAC recently advised that an MBS fee of $74.50 would be appropriate for PD-L1 testing to determine eligibility for PBS-subsidised pembrolizumab in patients with locally advanced or metastatic NSCLC.

Roche anticipated that a fee of $74.50 would also be appropriate for PD-L1 testing to determine eligibility for PBS-subsidised atezolizumab in patients with locally advanced or metastatic TNBC.

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

The IHC test 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 6 – PATHOLOGY SERVICES
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 triple negative breast cancer, to determine if the requirements relating to (PD-L1) expression status for access to atezolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $74.50

PART 9 – FEEDBACK

The Department is interested in your feedback.

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

Approximately 2 weeks

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

☒ Yes
☐ No

(b) If no, provide areas of concern:

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

Did not need to refer to the guidelines, most of the questions were self-explanatory.

☐ Yes
☒ No

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

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:

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