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): Insert corporation/partnership details here if relevant
Corporation name: Pfizer Australia Pty Ltd
ABN: **redacted**
Business trading name: Pfizer 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 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

Diagnostic testing for ROS proto-oncogene 1 (ROS1) rearrangements in non-small cell lung cancer (NSCLC) to determine eligibility for crizotinib treatment.

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)

Patients with non-squamous non-small cell lung cancer (NSCLC).

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)

Testing of tumour material in patients with non-small cell lung cancer (NSCLC) to detect chromosomal rearrangements in the ROS1 gene to determine eligibility for treatment with Xalkori (crizotinib) through the PBS.

PBS subsidy will also be sought for Xalkori (crizotinib) for the treatment of patients with ROS1-rearranged NSCLC.

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:

Insert relevant MBS item numbers here

(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:

The proposed test will determine eligibility for treatment with Xalkori (crizotinib) through the PBS.

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):

Crizotinib is currently PBS-listed for the treatment of anaplastic lymphoma kinase (ALK)-positive Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC). The PBS Item numbers for this indication are 10322G and 10323H.

A further application to the PBAC is planned for crizotinib for the treatment of ROS1-positive advanced NSCLC. <**REDACTED**>

(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

Insert PBAC submission item number here

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

Trade name: Xalkori
Generic name: Crizotinib

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 Sponsor believes that the single use consumables required to conduct a ROS1 FISH test are the same as those required for the existing ALK FISH testing.
Details of these consumables will be confirmed by seeking feedback from the identified pathology laboratories and presented in the full submission dossier.
Multi-use consumables: None

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: Pharmaceutical
Manufacturer's name: Pfizer Australia Pty Ltd
Sponsor's name: Pfizer Australia Pty Ltd

(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: 190963, 190964, 190965, 190966
TGA approved indication(s), if applicable: Xalkori is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).
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: **redacted**
Proposed indication(s), if applicable: **redacted**
Proposed purpose(s), if applicable: If applicable, insert description of proposed purpose(s) here

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.	Expansion cohort of a phase I (non-randomised) study	Shaw et al, 2014. Crizotinib in ROS1-Rearranged Non-Small-Cell Lung Cancer. NCT00585195.	A study of 50 patients with advanced ROS1-positive NSCLC. Patients were treated with crizotinib 250mg twice daily and assessed for safety, pharmacokinetics, and response to therapy. Crizotinib showed marked antitumor activity in patients with advanced *ROS1*-rearranged NSCLC. NCT00585195.	N Engl J Med 2014; 371:1963-1971 link to journal article	November 2014
2.	Observational study	Bergethon K. et al, 2012. ROS1 rearrangements define a unique molecular class of lung cancers.	Screening of 1,073 NSCLC tumour samples using a ROS1 FISH assay and correlation of clinical characteristics and overall survival with ROS1 status, and when available, *ALK* rearrangement status. In vitro studies assessed the responsiveness of cells with ROS1 rearrangement to the tyrosine kinase inhibitor crizotinib.	J Clin Oncol 2012;30(8):863-70. link to journal article	2012
3.	Observational study	Yoshida A. et al, 2013. ROS1-rearranged lung cancer: a clinicopathologic and molecular study of 15 surgical cases.	Study of 799 surgically resected NSCLCs by RT-PCR and FISH. Fifteen tumours harbouring ROS1 fusion transcripts (1.9% of tumours tested, 2.5% of adenocarcinomas) were identified. Affected patients were often younger non-smoking female individuals and they had overall survival rates similar to those of the ROS1-negative cancer patients.	Am J Surg Pathol 2013;37(4):554-62. link to journal article	2013

	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***
4.	Observational study	Cai et al, 2013. ROS1 fusions in Chinese patients with non-small-cell lung cancer.	Evaluation of the prevalence and clinicopathological features of *ROS1* fusions in patients with NSCLC. Screening was conducted on 392 samples using RT-PCR and validated by direct sequencing. *ROS1* fusions occurred in 8 (2.0%) patients and had no specific clinicopathological feature. ROS1-negative patients may have better survival than ROS1-positive patients.	Ann Oncol 2013; 24(7):1822-7. link to journal article	2013
5.	Observational study	Lee et al, 2013. ROS1 Receptor Tyrosine Kinase, a Druggable Target, is Frequently Overexpressed in Non-Small Cell Lung Carcinomas Via Genetic and Epigenetic Mechanisms.	IHC evaluation of expression of ROS1 kinase and its downstream molecules in 399 NSCLC cases, plus 92 recurrent cases. Overall expression rate of ROS1 was 22% in NSCLC. ROS1 expression was a worse prognostic factor for overall survival in adenocarcinomas of stage I NSCLC.	Ann Surg Oncol (2013) 20:200-208. link to journal article	2013
6.	Retrospective analysis	Fu et al, 2015. The frequency and clinical implication of ROS1 and RET rearrangements in resected stage IIIA-N2 non-small cell lung cancer patients.	Retrospective screening of a tissue microarray panel by FISH and confirmed by direct sequencing and IHC. The relationship between ROS1 or RET rearrangements, clinicopathologic features and prognostic factors were analysed. Of 204 cases, 4 were confirmed with ROS1 rearrangement. There was no significant association between ROS1 rearrangement and clinicopathological characteristics.	PloS ONE 10(4):e0124354. link to journal article	2015
7.	Part of a prospective phase II oligocentric trial.	Scheffler et al, 2015. ROS1 rearrangements in lung adenocarcinoma: prognostic impact, therapeutic options and genetic variability. NCT0218370	Study to genetically and phenotypically identify patients with ROS1-rearrangements within a molecular screening network. 1137 patients with adenocarcinoma of the lung were analysed for ROS1 status using FISH and NGS performed in positive cases. Clinical characteristics, treatments and outcome were assessed. Of the evaluable cases 19 (1.8%) were ROS1-positive.	Oncotarget. 2015 Apr 30;6(12):10577-85.	2015

	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***
8.	Study of diagnostic accuracy	Jin et al, 2015. Frequent aerogenous spread with decreased E-cadherin expression of ROS1-rearranged lung cancer predicts poor disease-free survival.	Study to evaluate the clinicopathological implications and histomorphological characteristics of ROS1-rearranged tumours and to investigate the diagnostic accuracy of ROS1 IHC. ROS1 characterisations were performed by FISH and ROS1 protein and E-cadherin expression by IHC using 754 NSCLC surgical specimens. ROS1 IHC correlated well with ROS1 gene rearrangement.	Lung Cancer 89 (2015) 343-349. link to journal article	2015
9.	Prospective non-interventional study	Chen et al, 2014. Clinical and the Prognostic Characteristics of Lung Adenocarcinoma Patients with ROS1 Fusion in Comparison with other Driver Mutations in East Asian Patients.	Multiplex RT-PCR was used to detect the ROS1 fusion gene and IHC was used to confirm expression of ROS1 in 492 lung adenocarcinoma cases. The demographic data and clinical outcomes of patients with the ROS1 fusion gene were compared with those of patients without the ROS1 fusion gene, including those with other driver mutations.	J Thorac Oncol. 2014; 9: 1171-1179. Link to journal article	2014
10.	Study of diagnostic accuracy and review of published literature	Viola et al: A Validation Study for the Use of ROS1 Immunohistochemical Staining in Screening for ROS1 Translocations in lung Cancer.	A cohort of lung tumours negative for other common mutations related to targeted therapies, enriched with four ROS1 cases first identified by FISH, were screened using IHC and FISH. A review of published data was also undertaken. IHC screening was 100% sensitive (95% CI: 48-100) and 83% specific (95% CI: 86-100) overall when an h-score >100 was used.	J Thorac Oncol. 2016 Jul;11(7):1029-39. link to journal article	2016
11.	Study of diagnostic accuracy	Scholl et al, 2013. ROS1 Immunohistochemistry for Detection of ROS1-Rearranged Lung Adenocarcinomas.	Study examining the correlation between ROS1 IHC and FISH and describing the clinicopathologic characteristics of ROS1-rearranged lung tumours. In 56 cases tested with both IHC and FISH, ROS1 protein expression in tumour cells was 100% sensitive and 92% specific for ROS1 rearrangements by FISH.	Am J Surg Pathol. 2013 Sep;37(9):1441-9. link to journal article	2013

	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***
12.	Study of diagnostic accuracy	Shan et al, 2015. Detection of ROS1 Gene Rearrangement in Lung Adenocarcinoma: Comparison of IHC, FISH and Real-Time RT-PCR.	Study to compare FISH, IHC and qRT-PCR assays for detection of ROS1 fusion in adenocarcinoma patients Among 60 cases, 16 (26.7%), 13 (21.7%) and 20 (33.3%) cases were ROS1-positive by IHC, FISH and qRT-PCR, respectively. Using FISH as a standard method, the sensitivity and specificity of IHC were 100% and 93.6%, respectively.	PLoS One. 2015 Mar 5;10(3):e0120422 link to journal article	2015
13.	Study of diagnostic accuracy	Cha et al, 2014. Screening of ROS1 Rearrangements in Lung Adenocarcinoma by Immunohistochemistry and Comparison with ALK Rearrangements.	Investigation of the diagnostic accuracy of ROS1 IHC across retrospective (n=219) and prospective (n=111) cohorts and a comparison of the diagnostic performance of ROS1 IHC and ALK IHC. Using an IHC-positivity cut-off of ≥2+, the sensitivity and specificity of ROS1 IHC were 100% and 95%, respectively.	PLoS One. 2014 Jul 24;9(7):e103333. link to journal article	2014
14.	Study of diagnostic accuracy	Mescam-Mancini et al, 2014. On the relevance of a testing algorithm for the detection of ROS1-rearranged lung adenocarcinomas.	Study of 121 triple negative lung adenocarcinomas and 80 additional cases with known EGFR, KRAS, PI3KCA, BRAF, HER2 mutations or ALK-rearrangement screened by IHC and FISH. Considering a positivity threshold of 2+ stained cells, the sensitivity of the ROS1 D464 antibody compared to FISH was 100% and the specificity 96.9%.	Lung Cancer. 2014 Feb;83(2):168-73. Link to journal article	2014

** 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.	A biology driven, trans-tumoral, multicentric phase II trial	Phase 2 Study Assessing Efficacy and Safety of Crizotinib in Patients Harboring an Alteration on ALK, MET or ROS1 (AcSé). NCT02034981.	Trial to assess the efficacy and the safety of the targeted agent crizotinib as a monotherapy in 23 cohorts of patients with identified activating molecular alterations in the crizotinib target genes. A cohort is defined by a pathology and a crizotinib-target alteration (eg gastric cancer with MET amplification).	Link to research	**Study Start Date:** August 2013 **Estimated Completion Date:** July 2019 **Estimated Primary Completion Date:** December 2016
2.	Phase II, single arm, open-label safety and efficacy study	Phase II Safety and Efficacy Study of Crizotinib in East Asian Patients With ROS1 Positive, ALK Negative Advanced NSCLC NCT01945021.	Study to assess treatment effectiveness and safety of oral crizotinib administered to East Asian patients with Advanced Non-Small Cell Lung Cancer (NSCLC) that is confirmed to be positive for a ROS1 positive gene mutation (translocation or inversion) and confirmed negative for an ALK mutation.	Link to research	**Study Start Date: September** 2013 **Estimated Completion Date:** July 2016

** 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):

Royal College of Pathologists (letter of support is attached)

Medical Oncology Group of Australia

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

Rare Cancers Australia (letter of support attached)

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

Not applicable

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

List relevant sponsor/s and or manufacturer/s here

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**

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:

In 2014 there were 11,580 new cases of lung cancer in Australia, representing approximately 9% of all cancer diagnoses that year. While this makes it the 5th most common cancer afflicting Australians, it was the number one cause of cancer-related mortality, accounting for 19% of cancer deaths in 2014 (AIHW 2014).

NSCLC accounts for about 85% of lung cancers and is a heterogeneous group of tumours of which adenocarcinoma, squamous cell carcinoma and large cell carcinoma comprise the major histological subtypes. Less than a third of NSCLC patients present with localised disease amenable to potentially curative surgical resection and NSCLC is associated with a 5-year survival of only 15% (Francis and Solomon 2010).

Cigarette smoking is the single largest cause of lung cancer, responsible for an estimated 90% of cases in males and about 65% of cases in females in Australia (AIHW, 2011). However, lung cancer in never-smokers is a frequent clinical entity which, when considered in its own right, is the seventh most frequent cause of cancer-related death worldwide (Francis and Solomon 2010).

Approximately 1% of NSCLC tumours manifest a rearrangement of the ROS1 oncogene which encodes an orphan receptor tyrosine kinase, which is related to anaplastic lymphoma kinase (ALK) and members of the insulin receptor family. As with ALK rearrangements, ROS1 gene rearrangements occur more frequently amongst patients with adenocarcinoma histology and in non- or light-smokers. However, at the genetic level, ALK and ROS1 rearrangements rarely occur in the same tumour, with each defining a unique molecular subgroup of NSCLC (Shaw et al., 2014). ROS1-positive NSCLC therefore represents an additional molecularly-defined subgroup which may be effectively treated with a specific targeted therapy such as crizotinib.

Information regarding the natural history of ROS1-positive NSCLC is limited, but several retrospective analyses describing the natural history of ROS1-positive NSCLC have been published. Whilst there are limitations and differences across these studies which need to be taken into account when interpreting the results, cumulatively, the findings seem to indicate that ROS1-positivity is unlikely to be a prognostic indicator in NSCLC, similar to what has previously been shown in ALK-positive NSCLC (Shaw et al., 2009, Shaw et al., 2011). It is therefore expected that ROS1 patients will have a poor 5-year survival, similar to the overall NSCLC population. A detailed systematic review all of the available evidence regarding the natural history of ROS1-positive NSCLC will be conducted by the Sponsor and provided in the submission.

There are currently no treatments either TGA approved, or listed on the PBS for the targeted treatment of patients with NSCLC who have ROS1 rearrangements.

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:

Who to test:

Patients with non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented absence of activating mutations of either the epidermal growth factor receptor (EGFR) gene or the anaplastic lymphoma kinase (ALK) gene.

When to test:

Pfizer proposes that ROS1 rearrangement testing is conducted at diagnosis. Given the low positivity rate of ROS1-gene rearrangements (approximately 1-2% of NSCLC patients) and the fact that EGFR, ALK and ROS1 rearrangements rarely occur in the same tumour, ROS1 FISH testing should be conducted as part of a screening algorithm sequential to the existing ALK and EGFR testing. Only those patients who are documented to be both ALK- and EGFR-negative should be eligible for the proposed service Medical Service for ROS1 gene rearrangement FISH testing.

In addition, it is proposed that patients will be pre-screened for evidence of ROS1 immunoreactivity by immunohistochemical (IHC) examination. Only those patients with documented evidence of a positive ROS1 IHC examination result, defined as a staining intensity score of 2+ or 3+, are to be eligible for the proposed medical service for ROS1 FISH testing.

How the patient is managed and referred:

In Australia, tumour tissue samples are collected by a respiratory physician/surgeons/interventional radiologist as part of routine clinical practice during the initial diagnosis of NSCLC patients. Two techniques; bronchoscopy, and percutaneous fine needle aspiration (FNA), are the most common. Bronchoscopy is preferred, as the amount of tissue obtained using FNA is often insufficient for molecular testing. FNA also carries greater risk of complications for the patient. The tissue samples are then sent to the Pathologists who perform the diagnostic testing.

Based on the outcome, the patient is referred back to respiratory physician/surgeon, or to a medical oncologist, who then communicates the clinical diagnosis. Medical oncologists may also request that the pathologists conduct additional molecular tests, in situations where the clinical profile, or results of the diagnostic report warrant further investigation.

In the majority of cases, the sample obtained during the initial biopsy is sufficient for conducting testing for both activating mutations of the EGFR gene and ALK gene rearrangement. Additional procedures are rarely required.

Patients with advanced NSCLC are referred to a medical oncologist for ongoing management.

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):

Treatment of locally advanced or metastatic NSCLC is evolving. Currently, patients with an initial diagnosis of non-small cell lung cancer (NSCLC) will have a tumour sample taken by the respiratory physician/surgeon/interventional radiologist when the initial diagnosis is conducted and this sample is sent for diagnostic testing for activating mutations of the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) gene rearrangement.

The current diagnostic testing algorithm for non-squamous NSCLC patients requires that EGFR mutation testing and ALK immunohistochemistry (IHC) screening are conducted first, the results of which are used to determine eligibility for PBS reimbursed treatments for advanced disease and / or further confirmatory diagnostic testing to confirm the patient's ALK status:

- Patients found to be EGFR-positive are eligible for initiation onto treatment with an EGFR inhibitor (either erlotinib or gefitinib) through the PBS once they have progressed to stage IIB or stage IV disease.

- Patients with an absence of activating mutations of the EGFR gene, plus documented evidence of ALK immunoreactivity by IHC examination may also be tested for ALK-gene rearrangements through fluorescence in situ hybridisation (FISH) testing of their tumour material through the MBS. A further core sample may be required for the ALK FISH testing in a minority of cases where the sample is of insufficient quality or quantity at the time of testing. Patients found to be ALK-positive in confirmatory FISH testing are eligible for subsidised treatment with crizotinib through the PBS once they have progressed to stage IIB or stage IV disease.

- Unselected locally advanced or metastatic NSCLC patients, with an absence of documented evidence of either EGFR or ALK-positivity are currently treated with a platinum based therapy in the first-line setting (most commonly carboplatin plus gemcitabine).

A flowchart of the current diagnostic flow is provided as an attachment to this application.

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

ROS1-gene rearrangements or the resulting fusion proteins may be detected in NSCLC tumour specimens using a number of different techniques, including; immunohistochemistry (IHC), fluorescence in situ hybridisation (FISH), reverse transcriptase polymerase chain reaction (RT-PCR) and next-generation sequencing (NGS). FISH was considered the gold standard assay for detection of ALK rearrangements and consequently, many early ROS1 screening studies used FISH as the predominant testing tool (Gainor and Shaw, 2013). FISH was also the predominant diagnostic method used in the Phase I/II study of crizotinib in advanced ROS1-rearranged NSCLC (Shaw et al., 2014).

The draft Molecular Testing Guidelines for the Selection of Lung Cancer Patients were recently published by the International Association for the Study of Lung cancer (IASLC), the College of American Pathologists (CAP) and the Association for Molecular Pathology (AMP) and are currently available for public comment. These draft guidelines recommend that, "ROS1 testing may use IHC as a screening test in lung adenocarcinoma patients; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method."

Feedback received from Australian Medical Oncologists and Pathologists indicates that the predominant testing approach for diagnosing ROS1-positive NSCLC in Australia is IHC examination, followed by confirmatory ROS1 FISH testing for cases with a positive IHC result. Accordingly, the medical service being proposed is for ROS1 FISH testing, which is to be conducted in cases with a positive result in ROS1 IHC pre-screening, with a positive IHC result defined as a staining intensity score of 2+ or 3+.

ROS1 FISH assays are performed on formalin-fixed paraffin-embedded (FFPE) tumour tissue. Several different ROS1 FISH assays have been developed, which generally use red or orange and green fluorescent probes to hybridise with sequences adjacent to or including a portion of the ROS1 gene, which is located on chromosome 6. In the absence of a ROS1 rearrangement, the overlapping probes produce a fused or yellow signal. When a ROS1 gene rearrangement is present however, the two probes become separated, resulting in a "split" signal. Isolated 3' signals can also be observed in the setting of ROS1 rearrangements. Specimens are deemed positive (rearranged) if more than 15% of tumour cell nuclei demonstrate split or isolated 3' signals (Gainor and Shaw, 2013, Rogers et al., 2015).

The whole process of conducting a FISH assay takes 2 days in total: sections need to be cut and there are long periods of processing, including overnight baking. A whole batch of cases can be done in this time, if required. Actual hands-on labour time is about 10 hours of scientist laboratory time per case (which could include a batch of many cases), 15-30 minutes scientist screening per case, plus approximately 30 minutes of pathologist reporting per case.

At present, testing for ROS1-positivity using FISH is only conducted in a minority of centres in Australia, including, but not limited to; the Royal Prince Alfred Hospital in Sydney, the Peter MacCallum Cancer Centre in Melbourne and St Vincents Hospital in Sydney. Details of a ROS1 FISH assay conducted at the Peter MacCallum Cancer Centre have been published (Rogers et al., 2015). Since there are currently no commercially available FISH tests for ROS1 testing in Australia (only ROS1 Break Apart FISH probes are commercially available at present), individual centres currently develop and validate their own modified 'in house' FISH protocols for detecting ROS1 rearrangements. The Sponsor intends to seek feedback from across the Australian laboratories that are conducting ROS1 FISH testing to inform MSAC decision-making.

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

No

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?

Not applicable

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):

Test:

It is proposed that any limitations on the funding of the medical service are consistent with the corresponding PBS restriction for the use of crizotinib. Proposed limitations include:

- NSCLC with non-squamous histology
- Negative test for EGFR and ALK

Pfizer believes that the ROS1-gene rearrangement is stable and is not affected by prior treatment, therefore each patient requires testing only once, with the exception of retests which would only be required if the sample is of insufficient quality or quantity at the time of testing.

Pharmaceutical:

It is proposed that patients receive crizotinib 250mg, twice daily, while patients have stable or responding disease.

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

Test: Tumour samples are already routinely collected for the existing genetic assessments used in treatment decision-making for advanced NSCLC patients (EGFR and ALK). Under the proposed algorithm, ROS1 FISH assays will only be conducted for those patients with a negative ALK test, therefore two FISH tests (ALK and ROS1) would only ever be required for those rare cases in which there is a false positive result on ALK IHC examination. It is not therefore expected that additional tumour samples will typically be required in order to conduct the proposed testing for ROS1 rearrangements.

Pharmaceutical: Not applicable.

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

Test: Medical oncologists and respiratory physicians will order ROS1 rearrangement testing and utilise the results in subsequent patient management. Pathologists will examine and interpret the results of sample testing.

Pharmaceutical: Crizotinib will be prescribed by a specialist medical practitioner.

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

Test: Not applicable (the service will always be provided by pathologists regardless of the health professional ordering the service).

Pharmaceutical: Not applicable.

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

Test:

Only medical oncologists or respiratory physicians will order ROS1-gene rearrangement testing and utilise the results in subsequent patient management.

Only pathologists will examine and interpret the results of sample testing.

Pharmaceutical:

Crizotinib may only be prescribed by a specialist medical practitioner.

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 proposed that testing should only be performed in laboratories that have received National Association of Testing Authorities (NATA) accreditation.

It is anticipated that ROS1 testing will be limited to specialised pathology laboratories based in major centres. Access to testing for patients in regional or remote areas would be facilitated by the collection of a tissue sample at their local treatment centre and transportation to an accredited pathology laboratory for testing.

The Sponsor is aware of 'Centres of Excellence' which currently perform the majority of ALK FISH testing. These centres have specialised laboratories capable of accurate and efficient processing of Australian ALK samples and it is anticipated that these same centres are also likely to become the 'Centres of Excellence' for ROS1 FISH testing in the future. The Sponsor can provide a list of these centres, if required.

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:

Describe rationale here

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):

Patients with advanced NSCLC are currently not tested for the presence of ROS1 rearrangements.

Patients with advanced NSCLC can currently receive testing to determine their EGFR status and ALK status, as a means of guiding therapy. The existing body of evidence indicates that EGFR mutation, ALK-gene rearrangements and OS1-gene rearrangements are mutually exclusive.

Patients with ROS1-rearranged NSCLC are not currently being routinely identified. 'no testing' will therefore be replaced by the new medical service which is being proposed in this co-dependant submission.

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

Specify item number/s here

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):

Current clinical management of advanced non-squamous NSCLC patients with an absence of evidence of an activating mutation of the EGFR gene or ALK rearrangement, in the absence of diagnostic testing for ROS1 rearrangement, is typically platinum-based therapy in the first-line setting (most commonly carboplatin plus gemcitabine), followed by pemetrexed or docetaxel (most commonly pemetrexed) as second-line treatment for advanced disease.

A flowchart of the current management of patients who receive the nominated comparator (no ROS1 testing) is provided as an attachment to this application.

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:

The proposed medical service will replace 'no testing' in eligible patients.

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):

The proposed flowchart for the management of patients in the presence of diagnostic testing for ROS1 gene rearrangement and crizotinib therapy for the treatment of the identified ROS1-positive patients is provided as an attachment.

It is proposed that patients will receive the proposed service for ROS1 testing at diagnosis following the existing testing for EGFR and ALK status. For patients with documented evidence of ROS1 rearrangement from IHC and confirmatory FISH testing, the first line treatment for advanced disease is changed in the proposed algorithm as ROS1-positive patients become eligible for crizotinib treatment through the PBS.

Upon progression on targeted treatment with crizotinib in the first-line setting, ROS1-positive patients are likely to receive a platinum doublet regimen (such as carboplatin plus gemcitabine), pemetrexed or docetaxel) in the second-line setting.

Unselected locally advanced or metastatic NSCLC patients with an absence of documented evidence of EGFR, ALK and ROS1-positivity will continue to receive platinum doublet therapy in the first-line setting (most commonly carboplatin plus gemcitabine), with pemetrexed or docetaxel monotherapy (most commonly pemetrexed) used in the second-line setting.

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):

The clinical claim made is that testing for ROS1 rearrangement and treating patients on the basis of the results of that test (patients with ROS1-positive NSCLC are treated with crizotinib; ROS1-negative patients or those not tested are treated with the current standard of care chemotherapy) is associated with clinical advantages (with respect to disease control) over the current scenario.

The proposed medical service (ROS1 testing) is therefore considered to be a clinically relevant diagnostic tool, due to its role in identifying a subset of NSCLC patients that is likely to benefit from treatment with targeted treatment (crizotinib).

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:
Adverse events
Treatment interruptions
Treatment discontinuations
Clinical Effectiveness Outcomes:
Objective tumour response rates
Duration of response
Progression-free survival
Overall survival
Quality-adjusted survival

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

	Cases	Assumption	Source
Incidence of lung cancer	11,573	Incidence rate (per 100,000) = 47.2	*Projected from AIHW ACIM Books 2016 (2012 dataset)*
Incidence of advanced lung cancer at diagnosis	8,101	70%	*Walters et al., 2012*
Incidence of recurrent lung cancer	530	1-year prevalence for patients diagnosed with localised disease = 63.2% recurrence rate = 28%	*Walters et al., 2012*
Total new advanced lung cancer cases / year	8,630	Sum of newly diagnosed and recurrent cases	
Incidence of non-squamous NSCLC	4,022	46.6%	*AIHW 2011*
Advanced non-squamous NSCLC patients who are both EGFR and ALK-negative	3,223	15% of patients are EGFR positive, 4.9% patients are ALK-positive	
ROS1-positive advanced non-squamous NSCLC patients	60	1.5% of NSCLC patients	*Gainor and Shaw, 2013*
Potential patients who could be eligible for the proposed service for ROS1 FISH testing	219	ROS1 IHC sensitivity and specificity of 100% and 95%, respectively	*Weighted average of identified studies using the proposed IHC positivity definition of +2 or +3 (Sholl et al., 2013, Shan et al., 2015, Cha et al., 2014, Mescam-Mancini et al., 2014)*

By using an IHC pre-screening test (similar to the strategy used for the current testing for ALK gene rearrangements NSCLC patients) the majority of patients who are ROS1-negative will be excluded. This will significantly reduce the resource requirements and time associated with the proposed ROS1 FISH testing.

Further details of these estimations will be presented in the submission dossier, which will include a comprehensive review of the available literature relating to the sensitivity and specificity of ROS1 IHC testing.

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

The Sponsor believes that ROS1 gene rearrangements are stable and not affected by treatment, therefore each patient will only require testing once. The only exceptions to this will be in the case of retests being required due to insufficient quantity and/or quality of the tumour sample to perform the analysis. An estimate of the number of retests that are likely to be required will be presented in the submission dossier.

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

Medical service: One test per patient (in year 1).

Pharmaceutical: It is anticipated that subsidised treatment of ROS1-positive patients with crizotinib through the PBS will continue to the point of disease progression.

In the pivotal study of crizotinib in ROS1-rearranged NSCLC patients, the median progression free survival (PFS) was 19.2 months (95% CI: 14.4 to not reached) and the median duration of treatment was 64.5 weeks (range, 2.3 to 182.0) with 30 patients (60%) continuing to receive treatment after the data cut-off date (Shaw et al., 2014).

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

Medical service: Assuming that ROS1 testing is first listed on the MBS in <**REDACTED**>, it is estimated that a total of <**REDACTED**>, patients would utilise the proposed medical service for confirmatory ROS1 FISH testing in the first full year of listing.

This estimate assumes that IHC pre-screening for ROS1 positivity has a sensitivity and specificity of 100% and 95%, respectively and a ROS1 testing rate of <**REDACTED**>, amongst eligible patients, based on the uptake of ALK testing in the first year of listing on the PBS/MBS.

The sensitivity and specificity assumption used in this calculation is based on a weighted average of the studies identified which report this information based on the proposed IHC positivity definition of +2 or + 3 (Sholl et al., 2013, Shan et al., 2015, Cha et al., 2014, Mescam-Mancini et al., 2014). A systematic review of all of the available literature regarding the sensitivity and specificity of IHC testing will be conducted and presented in the submission.

Pharmaceutical: <**REDACTED**>, patients (<**REDACTED**>, uptake amongst patients with a positive ROS1 FISH test in year 1 of listing).

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:

Medical service:

The anticipated numbers of patients who would receive the proposed medical service for ROS1 FISH testing in the first 3 years of listing (<REDACTED>,) are detailed in the table below.

	Number of patients	FISH uptake in eligible population
Year 1	**<REDACTED>**	**<REDACTED>**
Year 2	**<REDACTED>**	**<REDACTED>**
Year 3	**<REDACTED>**	**<REDACTED>**

Pharmaceutical:

The anticipated numbers of ROS1-positive patients initiating onto crizotinib in the first 3 years of listing are detailed in the table below.

	Number of patients	Uptake in eligible patients
Year 1	**<REDACTED>**	**<REDACTED>**
Year 2	**<REDACTED>**	**<REDACTED>**
Year 3	**<REDACTED>**	**<REDACTED>**

The Sponsor believes there is minimal chance of leakage beyond the proposed restriction, since NSCLC is an established disease area with experienced clinicians and clearly defined diagnostic criteria. Furthermore, crizotinib is already PBS-listed for the treatment of ALK-positive NSCLC patients for whom it also has evidence of clinical benefit.

PART 8 – COST INFORMATION

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

It is proposed that the cost of providing the medical service should be exactly the same as the current MBS fee for FISH testing for ALK-gene rearrangements:

Fee: $400 Benefit: 75% = $300.00 85% = $340.00

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

The whole process takes 2 days in total: sections need to be cut and there are long periods of processing, including overnight baking. A whole batch of cases can be done in this time, if required. Actual hands-on labour time is about 10 hours of scientist laboratory time per case (which could include a batch of many cases), 15-30 minutes scientist screening per case, plus approximately 30 minutes of pathologist reporting per case.

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: The following draft MBS item descriptor is based on the proposed testing algorithm for ROS1 rearrangement, in which patients have an IHC pre-screen, followed by confirmatory ROS1 FISH testing: Fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of ROS1 immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+, and with documented absence of either activating mutations of the epidermal growth factor receptor (EGFR) gene or anaplastic lymphoma kinase (ALK) gene rearrangement, requested by a specialist or consultant physician to determine if requirements relating to ROS1 gene rearrangement status for access to crizotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $**redacted**

Cognisant of the fact that genetic mutation testing in cancer is a rapidly evolving field, the Sponsor is willing to work with the Department of Health to finalise the details of the restriction.

PART 9 – FEEDBACK

The Department is interested in your feedback.

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

Approximately 4 weeks, including consultation with external experts together with the Sponsor's internal Medical team.

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