Australian Government

Department of Health

Application Form

(New and Amended

Requests for Public Funding)

(Version 2.4)

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.

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

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): Novartis Pharmaceuticals Australia Pty Ltd
Corporation name: Novartis Pharmaceuticals Australia Pty Ltd
ABN: 18 004 244 160
Business trading name: Novartis Pharmaceuticals Australia Pty Ltd

Primary contact name: ***REDACTED***

REDACTED

Alternative contact name: ***REDACTED***

REDACTED

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

☐ Yes
☒ No

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

☐ Yes
☐ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Expanding the BRAF testing MBS item to include patients with resectable Stage III melanoma.

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

Cutaneous melanoma is the most aggressive form of all skin cancers and has the highest rate of increasing incidence worldwide. It has been estimated that approximately 50% of melanomas harbour BRAF pathway-activating mutations. The introduction of the BRAF mutation inhibitors, dabrafenib and vemurafenib for the treatment of unresectable stage III and stage IV melanoma have led to significant progress (significant improvements in progression free survival and overall survival) for the treatment of these patients. Surgical resection is the treatment of choice for localised melanoma, and frequently cures patients with Stage I and Stage II disease. However, for patients diagnosed with resectable stage III melanoma, the outcomes are still poor, with estimated 5 year survival rates for Stage IIIA, IIIB and IIIC being 20%, 20% and 11% respectively. Consequently, adjuvant therapy is indicated for these patients with the intent of treating micrometastatic disease and reducing the risk of local and distant relapse.

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

The proposed medical service builds on the existing BRAF MBS item code, code 73336 (illustrated below), and simply requests that the word "unresectable" be removed. This change would provide reimbursed access to the BRAF test for all patients with Stage III and Stage IV metastatic melanoma; and thereby, reimbursed access for eligible patients to combination dabrafenib and trametinib in the adjuvant setting when the combination is approved for listing on the PBS. This change is in line with the results collected in the COMBI-AD trial, which demonstrates that patients with resectable Stage III and Stage IV melanoma treated with combination dabrafenib and trametinib experienced a significant reduction in their risk of relapse.

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

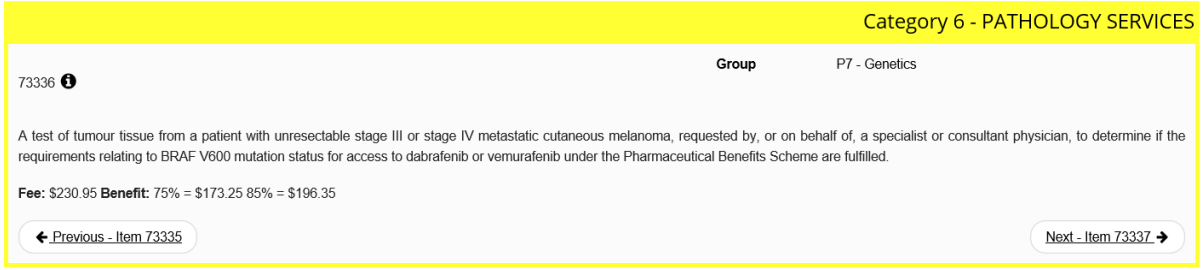
☒ Yes
☐ No

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

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

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

73336


Category 6 - PATHOLOGY SERVICES

73336 ⓘ

Group P7 - Genetics

A test of tumour tissue from a patient with unresectable stage III or stage IV metastatic cutaneous melanoma, requested by, or on behalf of, a specialist or consultant physician, to determine if the requirements relating to BRAF V600 mutation status for access to dabrafenib or vemurafenib under the Pharmaceutical Benefits Scheme are fulfilled.

Fee: $230.95 **Benefit:** 75% = $173.25 85% = $196.35

← Previous - Item 73335 Next - Item 73337 →

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

i. ☐ An amendment to the way the service is clinically delivered under the existing item(s)

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

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

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

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

☐ Yes
☒ No

(g) If yes, please advise:

7. What is the type of service:

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

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

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

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

☒ Pharmaceutical / Biological
☐ Prosthesis or device
☐ No

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

☐ Yes
☒ No

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

Insert PBS item code(s) here

(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

A PBAC submission for dabrafenib and trametinib use in the adjuvant setting, supported by data from the COMBI-AD trial, is planned for submission ***REDACTED*** in accordance with the co-dependent submission timelines.

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

Trade name: Tafinlar® and Mekinist®
Generic name: dabrafenib and trametinib

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

☐ Yes
X☐ 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
X☐ 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
X☐ 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

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

N/A

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

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

Type of therapeutic good: In-vitro diagnostic test
Manufacturer's name: Roche Diagnostics GmbH
Sponsor's name: Roche Diagnostics 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

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

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

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

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

ARTG listing, registration or inclusion number: 192394
TGA approved purpose(s), if applicable:

The primary use of the Cobas 4800 BRAF V600 Mutation test is the detection of the BRAF V600 mutations in DNA extracted from formalin fixed, paraffin embedded human melanoma and papillary thyroid carcinoma (PTC) tissue. In melanoma, it is intended to be used as an aid in selecting patients whose tumours carry BRAF V600 mutations for treatment with a BRAF inhibitor such as Zelboraf (vemurafenib) or Tafinlar (dabrafenib).

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

☐ 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

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

☐ Yes (please provide details below)
☐ No

Estimated date of submission to TGA: Insert date of submission here
Proposed indication(s), if applicable: If applicable, insert description of proposed indication(s)
Proposed purpose(s), if applicable: If applicable, insert description of proposed purpose(s) here

PART 4 – SUMMARY OF EVIDENCE

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

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*** **
1.	Phase III, Randomised controlled trial	Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma The pivotal trial upon which this publication is based is known COMBI-AD trial. NCT01682083 Primary investigator- Georgina Long	The trial sought to determine whether the combination of dabrafenib and trametinib would improve relapse-free survival, overall survival and freedom from relapse in patients with Stage III melanoma with BRAF V600E or BRAF V600K mutations after complete resection. The study is ongoing, but is not recruiting. 870 patients underwent randomisation.	http://www.nejm.org/doi/full/10.1056/NEJMoa1708539#t=article	September 10 2017

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

**** If the publication is a follow-up to an initial publication, please advise.*

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

	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.	**N/A**				

** 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

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

    Medical Oncology Group of Australia (MOGA)

    Clinical Oncology Society of Australia (COSA)

    Australia New Zealand Melanoma Trials Group (ANZMTG)

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

    N/A

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

    Melanoma Patients Australia

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

    Novartis do not produce or own the BRAF test. The tests in use in Australia and in the clinical trials are owned by 2 companies:

    Biomereaux and Roche

    Both were subject to assessment for the metastatic population, as per the assessment carried out for funding associated with vemurafenib use (MSAC application number: 1172) and dabrafenib use (MSAC application number: 1207) in patients with unresectable metastatic melanoma.

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

    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

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

Cutaneous melanoma is the most aggressive form of all skin cancers and has the highest rate of increasing incidence worldwide. In Australia in 2017 it was estimated that 13,941 patients would be diagnosed with cutaneous melanoma, and 1,839 patients would die of their disease.

Surgical resection is the treatment of choice for localised disease and frequently cures early Stage I and II disease. However, adjuvant therapy is indicated in patients with a high risk of recurrence following complete surgical resection with the intent of treating micrometastatic disease and reducing the risk of local and distant relapse. The risk of relapse and mortality is defined by independent predictive factors including primary tumor thickness, ulceration, mitotic rate, and lymph node burden (Balch et al, 2009). The overall 5-year relapse-free survival (RFS) rates observed for Stage IIIA, IIIB, and IIIC patients were 63%, 32%, and 11%, respectively. The estimated 5-year survival rates for Stages IIIA, IIIB, and IIIC from time of first relapse were 20%, 20%, and, 11%, respectively (Romano et al, 2010). According to a multivariate analysis, systemic relapse has been associated with a shorter survival than regional relapse, particularly for older patients and patients experiencing a symptomatic relapse. Of note, more than 40% of patients with Stage III melanoma will present with systemic disease at first relapse (observed in 40%, 51%, and 61% of patients with Stage IIIA, IIIB, and IIIC disease, respectively) (Romano et al, 2010).

The process of transformation of the melanocytes into invasive melanoma cells led to the discovery of numerous mechanisms responsible for growth and spreading of this disease. The RAS/RAF/MEK/ERK pathway (i.e., the mitogen-activated protein kinase [MAPK] pathway) is a critical proliferation pathway involved in normal cellular functions as well as many human cancers, including melanoma. It has been estimated that about 50% of melanomas harbor BRAF pathway-activating mutations, an important therapeutic target. With the availability of new therapies (including immune checkpoint inhibitors, agents targeting the BRAF V600 activating mutation and MAPK pathway), significant progress has been made for the treatment of metastatic melanoma, translating into improved progression-free survival (PFS) and overall survival (OS) outcomes. However, new therapies preventing the progression of resectable melanoma to metastatic melanoma are required. The results of a recent Phase III trial (known as the COMBI-AD trial) examining the efficacy of treatment with combination of dabrafenib and trametinib have shown that the risk of progression for patients with resectable stage III BRAF mutation positive melanoma can be reduced by up to 53% (Long et al 2017).

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

Large scale sequencing of the ERK pathway components has revealed a high frequency of mutations in human melanomas with approximately 40 to 60% of cutaneous melanomas found to harbour a mutation in the BRAF gene (Kudchadkar et al., 2012). The most common BRAF mutation in melanoma is BRAF V600E. This mutation results from a change in nucleotide sequence (GTG to GAG) in the BRAF gene and results in a valine to glutamic acid substitution in the translated gene product. This substitution leads to constitutive activation of the BRAF protein kinase. In a study of 308 Australian patients with metastatic melanoma, 73% of the mutations identified were BRAF V600E (Menzies 2012).

The second most common mutation in the BRAF gene is the BRAF V600K mutation. This mutation occurs in the same amino acid coding region as the BRAF V600E mutation, however it involves a change in two nucleotide residues (GTG to AAG). The V600K mutation results in a valine to lysine substitution in the translated gene product. In the study published by Menzies (2012) 19% of the mutations identified were BRAF V600K.

BRAF V600 mutations stimulate constitutive ERK signalling in cultured melanocytes, driving cell transformation and allowing the cells to proliferate in a growth factor-independent manner in vitro and as tumours in nude mice. In mouse models the expression of BRAF V600 mutations drives oncogenesis. Further, in human melanoma cells, RNA interference and small molecule inhibitors of BRAF and MEK have been used to show that BRAF V600 mutations are drivers of constitutive ERK and stimulates tumour proliferation (Dhomen and Marais, 2009).

Dabrafenib is one of several BRAF inhibitors demonstrated to display increased efficacy in BRAF mutant tumours. For this reason determination of the BRAF mutation status of melanoma tumours is important prior to commencing treatment with a BRAF inhibitor. The relationship between BRAF mutation status and a patient's response to treatment with BRAF inhibitors (including dabrafenib) leads to a co-dependent relationship between BRAF mutation testing and BRAF inhibitor treatment.

This submission requests that MSAC consider removing the requirement that a patient must have unresectable stage III or Stage IV melanoma to have a subsidised BRAF test, In accordance with the outcomes recently published for the COMBI-AD trial, patients with resectable Stage III melanoma will also benefit from treatment with a BRAF inhibitor if they are identified as BRAF mutation positive.

The investigation, management and referral of a patient with Stage III resectable melanoma will be similar to that experienced by a patient with Stage III unresectable melanoma. However, a patient with resectable Stage III melanoma will become eligible for a BRAF test earlier in the treatment algorithm; and the referral for the BRAF test will likely come more frequently from the surgeon in addition to the medical oncologist.

The request to broaden the reimbursement criteria for BRAF testing is based on the outcomes of the COMBI-AD trial. The COMBI-AD trial is a phase III, RCT that examined the efficacy and safety of dabrafenib in combination with trametinib in the treatment of patients with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high risk (Stage IIIA (lymph node metastases >1mm), Stage IIIB or Stage III C) cutaneous melanoma.

The characteristics of patients enrolled and treated in the COMBI-AD trial are not dissimilar to those patients enrolled and treated in the COMBI-D and COMBI-V trials previously assessed by MSAC for the metastatic populations. However, patients in the COMBI-AD trial were tested for BRAF mutation status earlier in the treatment algorithm and are therefore, marginally younger (50.4 years vs 54-55 years in the COMBI-V and COMBI-D trials. It is important to note that the proportion of patients diagnosed in the COMBI-AD trial with BRAF V600E and V600K mutations was comparable to the proportion diagnosed in the COMBI-V and COMBI-D trials, suggesting that the prevalence of these mutations is not different in the adjuvant population. There is no biological rationale as to why the prevalence rates of the BRAF mutation types would be any different between the populations.

It is clear from the previous DAPs for MSAC applications 1207 and 1172, the MSAC considered expanding access to BRAF testing to include patients with Stage III and Stage IV melanoma, but chose to specify patients with unresectable disease due to the availability of data for BRAF inhibitors in this population. With the availability of recent data from the COMBI-AD trial demonstrating a significant reduction in the relative risk of disease recurrence or death of 53%, it has become clear that adjuvant therapy with a BRAF inhibitor in this population is associated with a significant reduction in the number of patients progressing to metastatic disease. Despite the achievement of good outcomes with BRAF inhibitors and targeted therapies for patients with unresectable Stage III or metastatic disease, avoidance of progression to unresectable Stage III or Stage IV melanoma remains a highly desirable clinical outcome associated with an improved prognosis and therefore survival.

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

Currently in Australia, adjuvant therapy is not routinely provided to patients with Stage III resectable melanoma. A number of different therapeutics (e.g. ipilimumab and interferon) have been included in trials to explore the benefit/risk ratio for reducing the risk of disease progression in the adjuvant setting. Unfortunately, whilst these drugs were shown to provide a moderate improvement in relapse free survival and overall survival, the toxicity profile of each has meant that their use in Australia for the adjuvant therapy has been very limited. ***REDACTED*** No targeted therapies have been registered or

reimbursed for the treatment of resectable Stage III melanoma in Australia. Consequently, the vast majority of patients are being treated with a watch and wait approach.

The referral pathway is relatively complex for patients with melanoma. Essentially, a patient may present to a GP or dermatologist for an initial consultation. Suspicious looking moles, lumps or lesions will be sampled or where possible removed by the GP or dermatologist and a biopsy is sent to the pathologist for review. On a finding of melanoma, the cancer is staged and the margins inspected. For patients with Stage 1 or 2 melanoma with clear margins, no further action is taken and the patient is essentially treated with watch and wait. For patients identified with Stage 1 or 2 melanoma with unclear margins, further surgery will likely be performed – but the outcome of watch and wait remains. For patients identified with stage III disease, the patient will be referred directly to a surgeon; or to a surgeon via a medical oncologist for an assessment of the resectability of the tumour. If the residual tumour (or tumours) is/are considered resectable, the surgeon will remove it/them; and the patient will be referred back to the dermatologist or the medical oncologist for monitoring approximately every 6 months, for signs of progression to unresectable or metastatic disease.

Patients identified with unresectable or metastatic disease will be tested for the presence or absence of a BRAF mutation to determine their eligibility for chemotherapeutic intervention. In accordance with the current PBS prescribing restrictions, those patients testing positive for a BRAF mutation will be treated with a BRAF inhibitor or BRAF inhibitor/MEK inhibitor combination; whilst those patients testing BRAF negative will be treated with an immunotherapy. Patients who subsequently fail a BRAF inhibitor or BRAF inhibitor combination are then eligible to be treated with an immunotherapy. All patients who progress on an immunotherapy are eligible for further treatment with ipilimumab.

Please refer to Figure 1 for a schematic overview of the process outlined above.

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

Under the proposed base case testing scenario, BRAF mutation testing would be performed on patients diagnosed with Stage III resectable melanoma, in addition to patients with Stage III unresectable and Stage IV melanoma, already covered under MBS item 73331. The population eligible for testing under the base case scenario, as per the metastatic application, will be broader than the population eligible for dabrafenib, as those testing positive will have to meet further eligibility criteria (e.g. Completely resected, histologically confirmed high-risk [Stage IIIA (lymph node metastases >1mm), IIIB or IIIC; or those with initial resectable lymph node recurrence following diagnosis of Stage I or II melanoma]; with a known primary melanoma. Patients should have recovered from surgery and have an ECOG status of 0-1).

As previously outlined, diagnosis and tumour staging are made from biopsy samples which are expected to provide sufficient tumour material to also carry out BRAF v600 testing, consistent with current practice for patients with unresectable Stage III or Stage IV (metastatic) melanoma.

BRAF V600 testing would ordinarily be ordered by the patient's surgeon or oncologist once a diagnosis of high risk melanoma is made, however, in some cases reflex testing by the pathologist at the time of diagnosis may be considered. A surgeon, dermatologist or oncologist is typically responsible for the collection of a biopsy or cytological sample from the patient, although as previously described, general practitioners may also perform biopsies on melanoma patients. Tissue samples are normally processed into FFPE tissue blocks which are then sectioned, stained and mounted onto glass slides. Following mounting, samples are subsequently examined by a suitably qualified pathologist.

Once the tissue sample has been retrieved by the testing laboratory, an anatomical pathologist would mark the tumour; and a scientist would subsequently perform a dissection of the tumour cells (sample enrichment) so that an appropriate sample is available for DNA extraction and an assay would be performed by a molecular scientist or technician, under the supervision of a senior scientist or pathologist in accordance with NPAAC laboratory supervision standards. This is consistent with the process currently undertaken to process tumour samples in the metastatic setting.

All BRAF mutation tests must occur in NATA accredited laboratories. Competence to perform the test is already being monitored through an RCPA quality assurance program (QAP). As the test is already being

performed in the metastatic setting, no further investment in equipment is expected. A change in the number of tests being performed is expected as outlined later in this application.

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

N/A

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

N/A

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

The limitations on the provision of the test will be consistent with those currently in place for the metastatic setting. The majority of patients are expected to require only one BRAF test during their lifetime. Re-testing may be required if insufficient DNA is retrievable from biopsy cells, if the biopsy sample is not considered satisfactory (due to deterioration or formalin associated artefacts) or if DNA testing is inconclusive. As this application discusses treatment of population able to undergo a full tumour resection, the requirement for re-biopsy is considered low. As per the metastatic setting, only patients whose performance status is considered of an acceptable level for treatment (i.e. patients whose health status is considered sufficient to tolerate treatment) with dabrafenib in combination with trametinib will be considered eligible for BRAF V600 mutation testing.

Re-testing a patient for their BRAF mutation status following disease progression during or after cessation of adjuvant therapy with dabrafenib in combination with trametinib is not expected as the standard guidance for early and late progression and re-treatment for other solid tumours are considered to be applicable.

REDACTED

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

N/A

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

BRAF testing is currently undertaken in pathology laboratories. This is not expected to change with the addition of the resectable Stage III population.

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

N/A – this will be the same as for the unresectable Stage III and Stage IV (metastatic) patients

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

N/A – this will be the same as for the unresectable Stage III and Stage IV (metastatic) patients. Both surgeons and medical oncologists can currently refer patients with melanoma for a BRAF test.

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

N/A – this will be the same as for the unresectable Stage III and Stage IV (metastatic) patients.

36. (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

The BRAF test will be administered by the pathology department. Some tests will be conducted by hospital laboratories whilst others will be conducted in commercial pathology laboratories. This is consistent with what is currently taking place for patients with unresectable Stage III and Stage IV (metastatic) disease.

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

N/A

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

☒ Yes
☐ No – please specify below

As per the current testing landscape for patients with metastatic disease, BRAF testing is currently conducted in Australia.

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

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

Patients with resectable Stage III melanoma are not tested for their BRAF status in Australia. Consequently, the comparator in Australia is no test. Further, patients with resectable Stage III melanoma do not routinely receive adjuvant therapy and are consequently managed with watch and wait.

39. 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

40. 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 primary difference in the treatment algorithm if patients with resectable Stage III melanoma are eligible for BRAF testing will be provision of the test earlier in the treatment algorithm; and correspondingly, access to treatment with dabrafenib and trametinib in the adjuvant setting. This difference is illustrated in Figure 2.

As outlined in the results reported from the COMBI-AD trial, patients treated with dabrafenib and trametinib diagnosed with resectable Stage III melanoma experienced a 53% reduction in the relative risk of relapse or death, resulting in fewer patients progressing to unresectable Stage III and Stage IV (metastatic) disease. ***REDACTED***

Please refer to Figure 2 for further information.

41. (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:

Given the COMBI-AD trial reported a 53% reduction in the relative risk of disease progression or death with combination dabrafenib and trametinib therapy, it is likely that the majority of patients diagnosed with resectable Stage III melanoma will receive a BRAF test. ***REDACTED***

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

By testing patients with resectable Stage III melanoma for the presence/absence of the BRAF mutation, a population of patients will be identified for whom treatment with dabrafenib in combination with trametinib would likely be most effective. The recommended course of treatment for patients with resectable Stage III melanoma eligible for therapy is 150mg of dabrafenib twice daily in combination with 2mg of trametinib QD for a maximum period of 12 months, unless the patient experiences disease progression or treatment related toxicities. Data from the recently published COMBI-AD trial supports the efficacy of dabrafenib and trametinib in reduction of the risk of disease progression and death for patients with BRAF mutation positive resectable Stage III melanoma.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

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

Introducing BRAF testing for patients with resectable Stage III melanoma will satisfy a current unmet need and lead to the identification of a group of patients who will benefit from targeted therapy with dabrafenib in combination with trametinib. Reducing the number of patients who progress to having metastatic disease is a primary clinical treatment goal. Despite advances in the management of patients with metastatic melanoma, afforded by drugs including dabrafenib and trametinib, ultimately patients will still succumb to their disease.

The primary analysis of the COMBI-AD trial represents the first report of a randomised phase III trial evaluating adjuvant BRAF and MEK inhibitor combination therapy in patients with high-risk, resectable Stage III BRAFE/K positive melanoma.

Results from the COMBI-AD trial showed that the combination of dabrafenib and trametinib demonstrated superiority over placebo (watch and wait) for the primary endpoint of relapse free survival, for a population of patients with resectable stage III melanoma. A HR of 0.47 (95% CI: 0.39, 0.58), which was statistically significant, translates to a 53% risk reduction of disease recurrence or death in favour of dabrafenib and trametinib. The median follow-up time was 34 months in the dabrafenib+trametinib arm and 33 months in the placebo arm. The median estimate of RFS was not estimable for the dabrafenib+trametinib arm at the time of data cut-off due to the low event rate. In comparison, the time to median RFS was 16.6 months (95% CI: 12.7, 22.1 months). The RFS rates at 1, 2 and 3 years were consistently in favour of the dabrafenib+trametinib arm. The estimated RFS rates at year 3 were 58% in the dabrafenib+trametinib arm and 39% in the placebo arm.

As at the time of the primary analysis, 153 deaths had occurred (60 in the dabrafenib+trametinib arm; and 93 in the placebo arm), which is equivalent to only 26% of the total number of 597 deaths required for the final OS analysis. The median OS times in each group were not estimable due to the low event rates. 331 patients treated with dabrafenib+trametinib and 277 patients in the placebo arm were censored and are still being followed up for OS events.

REDACTED The combination of dabrafenib+trametinib reduced the risk of distant recurrence (HR= 0.51; 95% CI: 0.40, 0.65).

The estimated 53% reduction in the risk of recurrence or death with dabrafenib in combination with trametinib is considered to be clinically meaningful, representing an unprecedented improvement in RFS in a prospective, randomise, controlled trial in the adjuvant setting.

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

☒ Superiority
☐ Non-inferiority

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

The health outcomes upon which the comparative clinical performance of BRAF V600 mutation testing plus dabrefenib+trametinib versus the comparators of BRAF V600 testing + watch and wait or no BRAF testing + watch and wait will be measured include:

Safety Outcomes:

* toxic effects of subsequent treatment (e.g. skin rash, neutropenia, diarrhoea, pyrexia, fatigue, headache, nausea and vomiting)

* impact on patients of false positive and false negative test results

* rate of re-biopsy

* Adverse events related to biopsy

Clinical Effectiveness Outcomes:

* Relapse free survival
* Time to relapse
* Overall survival
* Quality of life
* Distant metastases free survival
* Freedom from relapse

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

In 2017, it is estimated that 13,941 patients will be diagnosed with melanoma of any grade. Also in 2017, it is expected that approximately 1,839 (13%) patients will die from melanoma.

Using the same methodology as was applied in the PBAC submission for the PBS listings of dabrafenib in combination with trametinib for the treatment of metastatic melanoma, including patients with stage III resectable melanoma is estimated to increase the population eligible for BRAF testing. As per the previous submission, due to a dearth of data describing the stage of the disease at which each patient is diagnosed and the subsequent progression rates, estimating the number of patients eligible for testing in the Stage III and Stage IV populations, including those patients with resectable Stage III disease, is challenging. As such, a number of assumptions was made as follows:

REDACTED

Table 1 – Estimate of the number of patients eligible for BRAF testing and treatment with a BRAF inhibitor if the restriction is expanded to include patients with resectable Stage III melanoma

REDACTED

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

As previously outlined in the response to Q30, it is anticipated that the majority of patients would only receive a BRAF test once in their lifetime.

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

As above, it is anticipated that the majority of patients would receive a BRAF test only once in their lifetime.

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

REDACTED

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

The estimated uptake of the proposed medical service over the 5 years from 2017 is shown in Table 1 above. No factors have been anticipated to impact the health systems ability to meet the needs of the proposed population as the test is already embedded in the pathology system.

There is no risk of leakage to populations not targeted by this service as the test is provided in a co-dependent capacity. It is clearly defined in the proposed restriction which patients are eligible to claim this service. The restriction clearly refers to payment only being provided for those patients with Stage III and Stage IV melanoma, as per the staging guidelines previously implemented for metastatic disease.

PART 8 – COST INFORMATION

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

REDACTED

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

The test will take the same duration of time for resectable Stage III patients as for patients with unresectable stage III/Stage IV disease.

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

The draft proposed MBS item descriptor is identical to that for item 73336, with the exception that the word "unresectable" has been removed. Given BRAF status does not identify a patient for a specific BRAF inhibitor; but as a patient who is a candidate for BRAF inhibition, any potential differences in the restrictions for the different BRAF inhibitors via the PBS should not impact the utilisation of the test. Further, as the current PBS listings for melanoma specify the use of MEK inhibitors (trametinib and cobimetinib) only in combination with BRAF inhibitors and not as monotherapy, inclusion of trametinib and/or cobimetinib in the restriction is not considered necessary.

Category 6 – PATHOLOGY SERVICES
Proposed item descriptor: a test of tumour tissue from a patient with stage III or stage IV metastatic cutaneous melanoma, requested by, or on behalf of, a specialist or consultant physician, to determine if the requirements relating to BRAF V600 mutation status for access to dabrafenib or vemurafenib under the Pharmaceutical Benefits Scheme are fulfilled. Fee: $230.95

PART 9 – FEEDBACK

The Department is interested in your feedback.

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

3 weeks

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

☒ Yes
☐ No

(b) If no, provide areas of concern:

There are areas of repetition and it may make sense in places for the applicant to provide information as the answer to one question, as opposed to three or four questions. This is perhaps most relevant for the patient number estimates.

56. (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

57. (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?

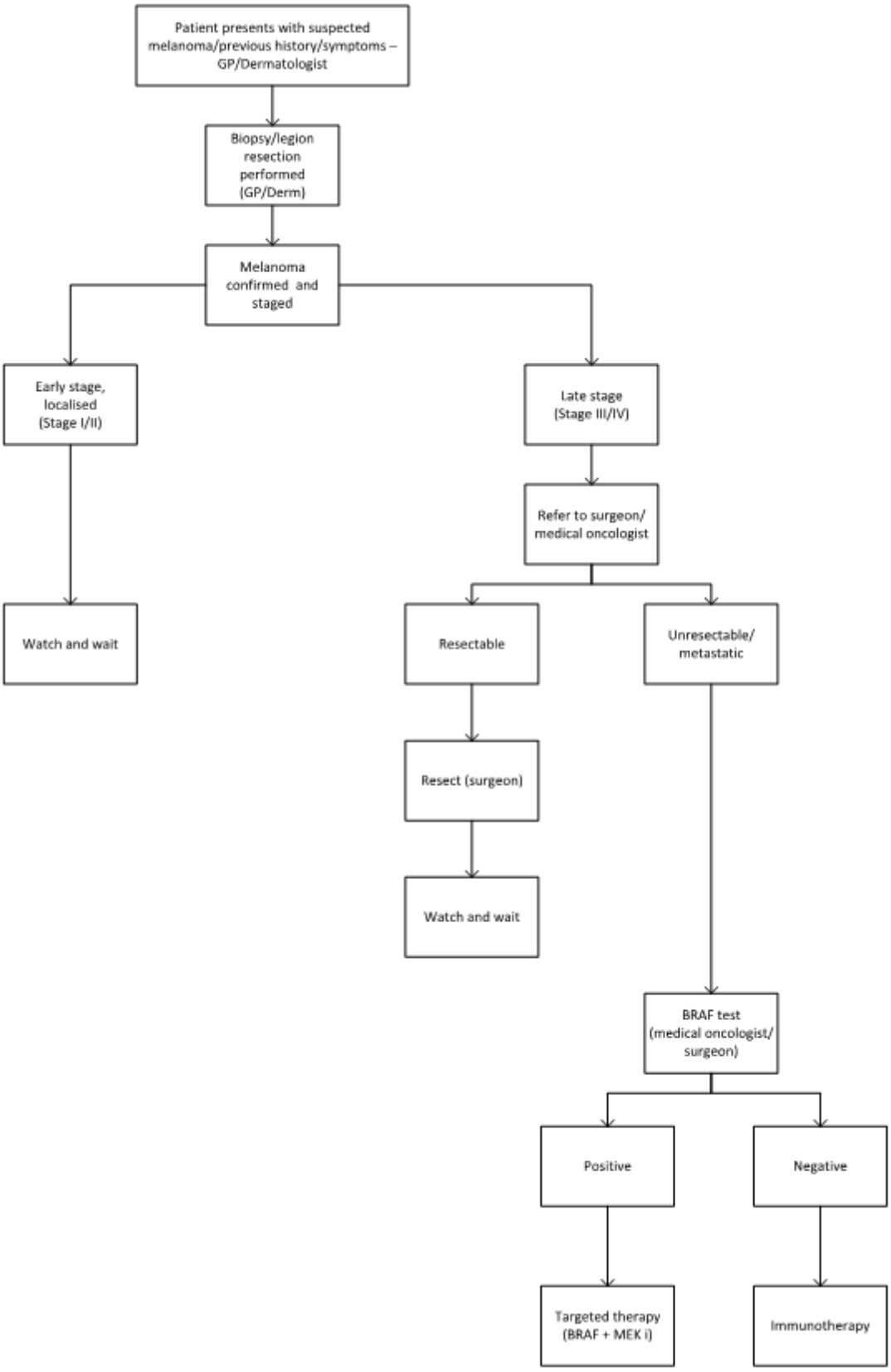
☐ Yes
☒ No

(b) If yes, please advise:

Insert feedback here

Attachment 1

Figure 1 – treatment algorithm in the absence of BRAF testing and dabrafenib and trametinib therapy for patients with resectable Stage III melanoma



Attachment 2

REDACTED