MSAC application 1804

Genetic testing to detect RET variants in patients with medullary thyroid cancer to determine eligibility for PBS subsidised selpercatinib treatment

Application for MBS eligible service or health technology

HPP Application number:

HPP200297

Application title:

Genetic testing to detect RET variants in patients with medullary thyroid cancer to determine eligibility for PBS subsidised selpercatinib treatment.

Submitting organisation:

ELI LILLY AUSTRALIA PTY LTD

Submitting organisation ABN:

39000233992

Application description

Succinct description of the medical condition/s:

Medullary thyroid carcinoma (MTC) is a rare form of thyroid cancer, arising from parafollicular C cells within the thyroid which are of neural crest origin. MTC is considered a neuroendocrine tumour (Gild 2023). REarranged during transfection (RET) mutations are genetic alterations found in 70% of MTCs (Wirth 2020). MTCs are either sporadic or hereditary (75-80% and 20-25% of presentations, respectively, Gild 2023). Hereditary MTC is due to an inherited condition called multiple endocrine neoplasia 2 or 3 (MEN2/3) and caused by germline RET mutations. Sporadic MTC is driven by somatic mutations, most commonly RET (50-60% of cases, Gild 2023; Parimi 2023). Current standard of care for patients with MTC is primarily surgery, which is only curative in approximately 40% of cases (Maxwell 2014). Patients with advanced or metastatic disease are treated with pharmacological interventions to treat symptoms and systemic therapies such as MKIs which are not PBS-listed for the treatment of MTC.

Succinct description of the service or health technology:

The proposed medical service is testing of tumour tissue in patients with MTC to detect RET mutations to determine eligibility for PBS-subsidised Retevmo® (selpercatinib). Selpercatinib is an oral, highly selective, small molecule inhibitor of the RET receptor tyrosine kinase, designed to target oncogenic RET mutations and fusions, making it a highly targeted therapeutic candidate for treating patients with

MTC that harbour a RET mutation.
This application does not nominate a specific methodology for RET mutation testing; however, it is anticipated that the majority of pathology laboratories will utilise polymerase chain reaction (PCR) or next-generation sequencing (NGS) panels to detect RET mutations in patients with MTC.

Application contact details

Are you the applicant, or are you a consultant or lobbyist acting on behalf of the applicant?

Applicant

Are you applying on behalf of an organisation, or as an individual?

Organisation

Applicant organisation name:

ELI LILLY AUSTRALIA PTY LTD

Application details

Does the implementation of your service or health technology rely on a new listing on the Pharmaceutical Benefits Scheme (PBS) and/or the Prescribed List?

Yes

Which list/schedule will the other health technologies be listed on?

Pharmaceutical Benefits Scheme

Is the application for a new service or health technology, or an amendment to an existing listed service or health technology?

New

Relevant MBS items

Please select any relevant MBS items.

MBS item number	Selected reason type

What is the type of service or health technology?

Investigative

Please select the type of investigative health technology: *(if investigative)*

Molecular diagnostic tests

Please select the type of molecular diagnostics health technology: *(if molecular diagnostics)*

Single gene assay

PICO set

Genetic testing to detect RET variants in patients with medullary thyroid cancer to determine eligibility for PBS subsidised selpercatinib treatment

State the purpose(s) of the health technology for this PICO set and provide a rationale: *(if investigative)*

Predictive

Purpose description:

To provide predictive information to support selection of a specific therapy or intervention.

What additional purpose(s) could the health technology be used for, other than the purposes listed above for this PICO set?

Purpose:

Prognosis

Purpose description:

To provide information about prognosis(staging/restaging)

Rationale:

This application seeks an MBS listing for RET mutation testing to determine eligibility for PBS-subsidised selpercatinib. Evidence suggests that somatic RET mutations are associated with poorer outcomes in MTC, including reduced overall survival, an increased risk of recurrence, and a higher likelihood of lymph node and distant metastases (Vuong et al. 2018). However, due to the limited therapeutic options available for MTC, the prognostic significance of RET mutations primarily serves to establish patient eligibility for treatment with an MKI. As such, the ADAR will not consider the prognostic outcomes of RET mutation testing.

Population

Describe the population in which the proposed health technology is intended to be used:

Medullary thyroid carcinoma (MTC) is a rare form of thyroid cancer, accounting for only 4% of all thyroid cancers (Cancer Australia 2024). It arises from parafollicular C cells within the thyroid, which are of neural crest origin, and hence MTC is considered a neuroendocrine tumour (Gild et al. 2023). MTC commonly presents with a thyroid nodule in the upper portion of the gland where C cells are primarily located, occurring in 75–95% of patients. Cervical lymphadenopathy is present in 70% of cases, and metastatic cervical lymphadenopathy occurring in 50% at initial presentation. Other symptoms include hoarseness, dysphagia, neck and throat pain. While 4–17% of cases have distant metastases affecting the brain, bones, lungs, or liver. Advanced MTC may cause diarrhoea and flushing as the tumour can secrete calcitonin and sometimes other hormonally active peptides (i.e., adrenocorticotropic hormone, calcitonin gene-related peptide) (Gild et al. 2023; Haddad et al. 2022).
REarranged during transfection (RET) mutations are genetic alterations found in patients with MTC and play a critical role in tumour development and progression. RET mutants are present in 70% of MTCs (Wirth et al. 2020). Patients harbouring more than 1 RET-mutant together with indels (insertion, deletion, or insertion and deletion of nucleotides in genomic DNA) or with indels alone present with more aggressive disease than those who do not (Gild et al. 2023).
MTCs are either sporadic (75-80% of presentations) or hereditary (20-25% of presentations) (Gild et al. 2023). RET mutations are pathognomonic in 98% of hereditary and 50-60% of sporadic (Gild et al. 2023; Parimi et al. 2023) MTCs.
Hereditary MTC is due to an inherited condition called multiple endocrine neoplasia 2 or 3 (MEN2, MEN3; formerly MEN2A, MEN2B), a condition that can cause tumours affecting the endocrine glands. In patients with a suspected clinical diagnosis of

MEN2 or 3, either due to suspected MTC or another tumour type, detection of germline mutations in the RET gene is standard practice, as MEN2/3 results from germline mutations in the RET proto-oncogene. Patients with hereditary MTC typically present with bilateral tumours. Pheochromocytoma occurs in 40-50% of patients with MEN2A or MEN2B. Primary hyperparathyroidism is present is 10% to 25% of patients with MEN2A, but is absent in MEN2B. MEN2B is uniquely associated with marfanoid habitus, kyphoscoliosis/lordosis, joint laxity, mucosal neuromas typically at lips and tongue, and intestinal ganglioneuromas (Block et al. 1980; Eng C 1999; Yasir M et al. 2023).

Sporadic MTC is driven by somatic mutations, most commonly in RET (50-60% of cases) or RAS genes (Gild et al. 2023; Parimi et al. 2023). The most common somatic RET mutation is M918T (p.Met918Thr), which is associated with a more aggressive disease course and poor prognosis with increased risk of lymph node metastases, advanced tumour stage, and recurrence. Other RET mutations, include mutations in multiple other codons (883, 634) and deletions. In cases where RET mutations are absent, somatic RAS mutations (most commonly HRAS p.Gln61Arg) are often present, and these are generally associated with less aggressive tumour behaviour (Gild et al. 2023). Patients with sporadic MTC generally present with unilateral tumours and no other endocrine involvement (Block et al. 1980; Somnay et al. 2013)

RET mutation status is required to determine eligibility for selpercatinib treatment. The target population for this application is patients with a confirmed clinical diagnosis of RET-positive mutant MTC. This submission relates to the co-dependent technology, RET mutation testing to determine eligibility for PBS-subsidised treatment with selpercatinib.

Select the most applicable Medical condition terminology (SNOMED CT):

Medullary thyroid carcinoma

Intervention

Name of the proposed health technology:

Tumour tissue testing for RET gene mutations to determine eligibility for Retevmo® (selpercatinib)

Comparator

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). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

Test: As testing for RET mutations is not currently funded for MTC patients, the comparator would be 'no MBS-funded RET mutation testing'.
Treatment: The current standard care for patients with a clinical diagnosis of MTC is primarily surgical intervention, and in cases of advanced or metastatic disease, patients are treated with pharmacological interventions to treat symptoms and systemic therapies such as MKIs.

Outcomes

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

As a result of a positive RET tumour tissue test, a change in clinical management would occur. Patients who harbour a RET mutation would be eligible to receive selpercatinib on the PBS, resulting in improved health outcomes such as increased progression-free survival and overall survival.

Clinical utility of test:
Treatment effect modification of selpercatinib in MTC patients with a RET mutation status (predictive validity).
Longitudinal accuracy outcomes
Other test-related considerations:

- Test turn-around time
- Estimated number of patients being tested
- Number needed to test
- Cost of testing per patient

Clinical effectiveness outcomes:

- Progression free survival (PFS)
- Overall survival (OS)
- Overall response rate (ORR)
- Comparative tolerability

The LIBRETTO-531, LIBRETTO-001 and LIBRETTO-121 trials demonstrated that treatment with selpercatinib led to a clinically meaningful reduction in disease progression and survival benefits in treatment-naïve, pre-treated, adolescent, and paediatric patients with advanced RET-mutant MTC. Additionally, the LIBRETTO-531 trial showed that selpercatinib had better tolerability compared to current standard of care with MKIs, an important factor in prolonging treatment duration and delaying progression of the disease.

Proposed MBS items

Proposed item:

AAAAA

MBS item number (where used as a template for the proposed item):

MBS item 73339 and 73437 used as a template for the proposed item descriptor.

Category number:

PATHOLOGY SERVICES

Category description:

GENETICS

Proposed item descriptor:

Detection of mutations in the RET gene in patients with a clinical diagnosis of medullary thyroid cancer requested by a specialist or consultant physician who manages the treatment of the patient to determine access to specific therapies relevant to these mutations listed on the Pharmaceutical Benefits Scheme (PBS).

Proposed MBS fee:

$400.00

Indicate the overall cost per patient of providing the proposed health technology:

$400.00

Please specify any anticipated out of pocket expenses:

$0.00

Provide any further details and explain:

No additional out-of-pocket costs are expected.

How is the technology / service funded at present? (For example: research funding; State-based funding; self-funded by patients; no funding or payments):

RET mutation testing services are provided in public hospitals funded under state and territory hospital funding arrangements. Somatic RET mutation testing is also commercially available in Australia through private pathology providers, however, it is only offered as part of a comprehensive somatic mutation panel rather than a standalone test. Australian Clinical Labs provides this service for a non-Medicare rebatable fee of $750. Alternatively, Sonic Genetics offers a more extensive thyroid-related gene panel, including RET, at a non-Medicare rebatable fee of $2,100 for a single nodule and $1,164 for each additional nodule (Australian Clinical Labs 2023; Sonic Genetics). The proposed MBS fee of $400 is consistent with other MBS listed pathology services for mutation testing in a single gene for a test of tumour tissue (e.g item 73338 for RAS mutation testing) and is consistent with the fee for MBS item 73339 for detection of germline mutation in the RET gene. RET mutation testing offered by Sonic Genetics and Australian Clinical Labs is priced higher than the proposed item, as these tests include broader mutation panels.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

Superior

Please state what the overall claim is, and provide a rationale:

RET mutation testing, followed by targeted treatment with selpercatinib is superior to no MBS-funded RET mutation testing and standard of care.
This application proposes that RET mutation testing, as a co-dependent technology, is necessary to determine treatment eligibility for selpercatinib in patients with confirmed diagnosis of MTC. The use of RET mutation testing, followed by treatment with selpercatinib in eligible patients, results in superior health outcomes and a manageable safety profile compared to no MBS-funded RET mutation testing' and treatment with the current standard of care.
This clinical claim is supported by the selpercatinib clinical trials presented in the PBAC submission. The pivotal trial LIBRETTO-531 demonstrated superior efficacy and an acceptable safety profile for selpercatinib compared to MKIs cabozantinib and

vandetanib in advanced or metastatic RET-mutant MTC. Patients receiving selpercatinib had a clinically meaningful and statistically significant reduction by 80% in the hazard of disease progression or death, along with a superior PFS rate compared to the control arm. The PFS rate at 36 months was 64.1% in selpercatinib arm versus 21.7% in the control arm. In addition, patients receiving selpercatinib reported less AEs requiring permanent discontinuation, reflecting in a longer time to TFFS in comparison to the control arm (63.8% vs. 19.2%, respectively).
The necessity of RET mutation testing is reinforced by the clinical utility of the test, as selpercatinib is a highly selective RET inhibitor and only effective in patients with a confirmed RET mutation. RET mutation testing ensures appropriate patient selection preventing the use of selpercatinib in patients unlikely to benefit, thereby optimising treatment outcomes and improving overall clinical management.

Estimated utilisation

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

The use of RET mutation testing is standard practice in Australia for MTC and is conducted and billed under state and territory public hospital arrangements (Newton S et al. 2013). This trend has not changed since 2013 when the Assessment Report for MSAC 1152 stated that "Diagnostic RET mutation testing is standard practice, such that the number of newly diagnosed MTCs each year is a useful proxy for the estimated number of diagnostic RET mutation tests performed annually" (Newton S et al. 2013). Therefore, 100% of newly diagnosed patients per year is expected to uptake the proposed health technology. In 2024, 4,335 patients were projected to be diagnosed with thyroid cancer (Australian Institute of Health and Welfare 2024). A total of 4% of thyroid cancers will be attributable to the diagnosis of MTC (Cancer Australia 2023).
Patients accessing RET mutation testing will also be required to meet the criteria of the PBS restriction for selpercatinib. The proposed PBS restrictions require patients to have advanced or metastatic MTC, with progressive and symptomatic stable disease that is responding to treatment with selpercatinib. The method for calculating number of patients with MTC who will access RET mutation is shown in the attached utilisation calculation reference workbook. As RET mutation testing is currently standard practice under state and hospital funding models, it is assumed that prevalent MTC patients will have predetermined RET status, and MBS funded RET mutation testing will be primarily accessed by incident patients.
The projected incidence of MTC for the years 2026-2031 was estimated using the average growth rate of MTC incidence from the last five years (2020-2024), calculated

at 4.35%(Australian Institute of Health and Welfare 2024). This growth rate was applied to the incidence population from the previous year, resulting in an estimated 189 newly diagnosed patients in 2026, increasing to 234 newly diagnosed patients in 2031.
As patients with T stage T1-T2 disease may also have advanced nodal involvement (N1a, N1b), extra nodal extension, or metastatic disease, this proportion was based on the population classified as stage I or II by AJCC stage classification. As such, 46% were classified as patients with T stage T1-T2, 45% with advanced disease and 9% with metastatic disease (Papachristos et al. 2023). These proportions were applied to calculate the number of patients at each disease stage
Patients progressing from stage T1-T2 to metastatic disease was determined as the annual survival rate of patients progressing from stages T1a-T3 to stage T4 (3.9%) multiplied by the proportion of patients with stage T1-T3 disease who are stage T1-T2. Accordingly, 2% of patients will progress from stage T1-T2 to metastatic disease
RET mutation testing via polymerase chain reaction (PCR) or next-generation sequencing (NGS) is conducted on tumour specimens and is expected to be conducted as a part of standard clinical management. Therefore, 100% of the incident population each year is expected to uptake the proposed technology, RET mutation testing. Based on the above methodology, 189 patients are expected to access RET mutation testing in 2026.

Provide the percentage uptake of the proposed health technology by the proposed population:

Year 1 estimated uptake (%):

100

Year 2 estimated uptake (%):

100

Year 3 estimated uptake (%):

100

Year 4 estimated uptake (%):

100

Estimate the number of patients who will utilise the proposed technology for the first full year:

189

Optionally, provide details:

The projected incidence of MTC for the proposed years of listing (2026-2031) was estimated using the average growth rate of MTC incidence from the last five years (2020-2024) (Australian Institute of Health and Welfare 2024), calculated at 4.35%. This rate was applied to the projected number of MTC patients in 2024 (n=173) to estimate the incidence in 2025 (n=181) and 2026 (n=189). RET mutation testing, alongside germline testing, is expected to be a standard part of clinical management. As a result, 100% of the incident population is anticipated to undergo RET mutation testing.

Will the technology be needed more than once per patient?

No, once only

Consultation

List all entities that are relevant to the proposed service / health technology. The list can include professional bodies / organisations who provide, request, may be impacted by the service/health technology; sponsor(s) and / or manufacturer(s) who produce similar products; patient and consumer advocacy organisations or individuals relevant to the proposed service/health technology.

Entity who provides the health technology/service

- The Royal College of Pathologists of Australasia (RCPA)
- The Australian Genomic Cancer Medicine Centre (AGCMC)

Entity who requests the health technology/service

- Private Cancer Physicians of Australia (PCPA)
- The Australian Genomic Cancer Medicine Centre (AGCMC)
- The Medical Oncology Group of Australia (MOGA)
- The Royal College of Pathologists of Australasia (RCPA)

Entity who may be impacted by the health technology/service

- Private Cancer Physicians of Australia (PCPA)
- The Australian Genomic Cancer Medicine Centre (AGCMC)
- The Medical Oncology Group of Australia (MOGA)
- The Royal College of Pathologists of Australasia (RCPA)

Entity relevant to the proposed service/health technology

- Australian Society of Otolaryngology Head and Neck Surgery (ASOHNS)
- Australian Thyroid Foundation (ATF)
- Endocrine Society of Australia (ESA)
- Rare Cancers Australia
- Thyroid Cancer Survivors Association

Regulatory information

Would the proposed health technology involve the use of a medical device, in-vitro diagnostic test, radioactive tracer or any other type of therapeutic good?

Yes

Has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)? *(if 'Yes' above)*

No

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

No

Is the intended purpose in this application the same as the intended purpose of the ARTG listing(s)?

No

Is the therapeutic good to be used in the service exempt from the regulatory requirements of the Therapeutic Goods Act 1989?

No

Is the therapeutic good classified by the TGA as for Research Use Only (RUO)?

No

Is the therapeutic good in the process of being considered by the TGA? *(if 'Yes' above)*

No

Please provide details of when you intend to lodge an ARTG inclusion application, or provide a rationale if you do not intend to lodge an ARTG inclusion application: *(if 'No' above)*

This application does not nominate a specific test or test methodology and it is anticipated that both commercial in-vitro diagnostic medical devices (IVD) registered on the Australian Register of Therapeutic Goods (ARTG) and in-house IVDs would be utilised, with reliance on testing being performed in laboratories holding the appropriate National Association of Testing Authorities (NATA) accreditation.

Codependent details

Will a submission be made to the Pharmaceutical Benefits Advisory Committee (PBAC)?

Yes

Please provide a rationale for the codependency and indicate how the proposed PBS restriction would reference the intervention(s) proposed for MSAC consideration:

It is proposed that all patients diagnosed with MTC will undergo testing for rearranged during transfection (RET) mutation. Patients who test positive to a RET mutation would then be eligible for access to PBS-subsidised selpercatinib. The proposed PBS restriction will include a clinical criteria stating that the condition must have evidence of RET mutations, and that this evidence must have been obtained prior to commencing selpercatinib treatment.
Patients with a suspected clinical diagnosis of MEN2 can access germline RET mutation testing under MBS item 73339. This item is not considered a prerequisite test for RET mutation testing proposed in this application. Patients with suspected MEN2 have distinct clinical characteristics which are identifiable to treating clinicians, making negative results uncommon. The sponsor proposes the new MBS is not specific for somatic RET mutations. As RET mutation testing for access to selpercatinib will be conducted on tissue, it can identify germline mutations that may have been missed or be replacement for MBS item 73339 in a patient who otherwise meets eligibility criteria for selpercatinib.
The pivotal trial to be presented in this submission LIBRETTO-531 demonstrated that patients RET-mutant MTC treated with selpercatinib experience significant clinical benefit including a reduction in the hazard of disease progression or death compared to MKIs cabozantinib or vandetanib (Hadoux 2023). In the absence of RET

mutation testing, this targeted treatment would not be available, resulting in patients receiving standard of care. Currently, standard of care includes surgery as the primary treatment, and in cases of advanced or metastatic disease, pharmacological interventions to treat symptoms and systemic therapies such as MKIs through private or off-label use. Thus, testing for a RET mutation followed by targeted treatment with selpercatinib is expected to lead to significant improvements in health outcomes for MTC patients.