

MSAC REAPPLICATION TEMPLATE

Reapplication Name:	Genetic testing to detect AKT-pathway alterations in patients with hormone receptor-positive, HER2-negative advanced breast cancer
Previous application number	1766
Name of previous application	Genetic testing to detect AKT-pathway alterations in patients with hormone receptor-positive, HER2-negative advanced breast cancer, to determine eligibility for PBS subsidised capivasertib

A. Funding Source

1. Please check the box that corresponds with the program through which the health technology would be funded:

- ☒ Medicare Benefits Schedule (MBS). Please:
- a) Upload an in principle Statement of Clinical Relevance¹ when uploading this template.
 - b) Note in [Table 2](#) below, any changes to the proposed MBS item(s) compared to the previous ADAR.
- ☐ National Blood Agreement.
- ☐ National Health Reform Agreement Addendum (high-cost, highly specialised therapies).
- ☐ National Diabetes Services Scheme.
- ☐ Other. Please specify the funding program:

2. Has the funding source changed compared to your previous application?

- ☒ No

B. Regulatory Information

1. Does your proposed service or technology involve (check as many as applicable):

- ☐ the use of a medical device, *in-vitro* diagnostic test, radioactive tracer, or any other type of therapeutic good? Please complete the section titled [B1: ARTG Listing](#).
- ☒ a service or laboratory requiring accreditation by the National Association of Testing Authorities (NATA)? Please complete the section titled [B2: NATA Accreditation](#).
- ☐ an MBS item descriptor that refers to a specific radiopharmaceutical or a set of radiopharmaceuticals? Please complete the section titled [B3: Radiopharmaceuticals](#).
- ☐ None of the above. Proceed to the [Other information](#) section.

¹ The in principle Statement of Clinical Relevance demonstrates 'in principle' support for the proposed service. This must be from the most relevant professional medical/health group (i.e., an official college or society) that represents practitioners who would **perform** the proposed services, and (in the case of investigative technologies only) practitioners who would **request** the proposed service.

[B1: ARTG Listing](#)**2. Has the proposed health technology been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?**☐ No (Go to question 4)☒ Yes. Please state the ARTG ID, TGA approved indication(s) and TGA approved purpose:

ARTG ID:	407960/407961
TGA approved indication(s):	Currently approved label: TRUQAP is indicated in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer following recurrence or progression on or after an endocrine based regimen. Proposed label change effective end of July 2026: <i>TRUQAP, in combination with fulvestrant, is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)- negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN- alterations following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.</i>
TGA approved purpose:	

3. Is the intended purpose in this reapplication the same as the intended purpose of the ARTG listing?☒ Yes. Go to the next applicable section ([B2: NATA Accreditation](#); [B3: Radiopharmaceuticals](#); or [Other Information](#)).

B2: NATA Accreditation

Where applicable, laboratories and other investigative service providers must be accredited by [NATA](#). The scope of NATA accreditation must capture the service for which reimbursement is being sought.

Please provide details of NATA accreditation, clearly demonstrating that the services or technologies included in your MSAC reapplication are in-scope of the accreditation. Where accreditation is not yet in place, provide documentation demonstrating that the accreditation process is underway. Provide anticipated timeframes for the NATA accreditation decision.

The Roche AVENIO CGP assay identifies PIK3CA/AKT1/PTEN alteration status and is currently available at and in use by Monash and Sonic/Sullivan & Nicolaides. Monash Pathology and Sonic/Sullivan Nicolaides intend to extend the scope of their accreditation to the Therapeutic Goods Administration to include the Roche Avenio CGP V2 assay as a class III in-house IVD for identifying PIK3CA/AKT1/PTEN alteration status by the next annual review.

Table 1: Summary of key matters of concern

COMPONENT	MATTER OF CONCERN	HOW MATTER WILL BE ADDRESSED IN ADAR
Claim of co-dependency	Overall, MSAC considered the co-dependency claim is likely to be reasonable but needed further justification, because the trial results suggested that patients appeared to have some PFS benefit from CAPI irrespective of whether their tumours had a AKT pathway alteration, and because the key evidence demonstrating a PFS benefit was based on post hoc analyses. MSAC considered that based on the current evidence, it might be inequitable to exclude non-AKT pathway altered patients from access to treatment. MSAC advised that further evidence would be required to confirm if AKT pathway alteration is a treatment effect modifier, and therefore to better support the clinical claim of codependence (1766 PSD, p7).	The TGA have restricted the TGA label to patients with demonstrated PIK3CA/AKT1/PTEN pathway alterations. The rationale from the Delegate's Overview is provided below: Redacted <i>Capivasertib is a targeted therapy with a clear biological rationale linked to PI3K-AKT-PTEN pathway alterations. Given the absence of an OS benefit, and the suggestion of possible harm in patients without pathway alterations, it appears necessary to reconsider the current broad indication.</i>
Rate of missed alterations in 'known non-AKT pathway altered' group		This issue may not be relevant given that the TGA label restricted to AKT altered pathway gene variants, given non-AKT altered pathway group is not eligible for treatment.

Justification for Comprehensive Genomic Profiling (CGP) and therefore cost of testing	MSAC considered that the proposed fee was reasonable only if comprehensive genomic profiling (CGP) testing was performed and required. However, MSAC considered that the need for CGP testing was not clearly justified, as the testing would be performed for 3 genes only and more targeted options for testing were available, which could reduce both costs and failure rates. MSAC advised that a re-application should provide further information around the need for CGP or, alternatively, propose a more targeted testing option and revise the proposed fee (1766 PSD, p6)	CGP is required to identify all patients who may be eligible for treatment with capivasertib, consistent with the testing approach used in the CAPItello-291 trial. The PSD references the prices of MBS item 73296 (targeted assay to identify BRCA gene variants) and 73437 (to identify point mutations such as EGFR), however both tests target hotspots on the gene. If these same targeted, smaller assays are used to detect AKT pathway alterations, you will not detect PTEN in approximately 10% of patients with clinically relevant PTEN single nucleotide variants. Consultation with an Australian laboratory has indicated that CGP can now be provided at a cost of approximately \$1,900 per test, which is \$300 lower than the cost proposed in the original submission (\$2,200). CGP represents the most appropriate testing method to support equitable access to capivasertib for all eligible patients due to its ability to comprehensively detect all AKT pathway alterations including all PTEN variants.
Revised Economics around failure rate	The ESCs noted that the model assumed a test failure rate of 5% despite a failure rate of 15% in CAPItello-291, and that evidence was not provided to justify this assumption. The ESCs noted that the pre-sub-committee response stated that this was considered appropriate by a local clinical expert; however, as the test to be used in Australia is uncertain, the ESCs considered that there was not sufficient evidence to justify the lower test failure rate (1766 PSD, p47)	With the price discount proposed in the February 2025 PBAC resubmission, the ICER remains cost-effective in all scenarios, including when failure rates are increased from 5% (in the submitted model) to 15% (as reported in CAPItello-291).

Table 2: Summary of changes to PICO criteria since previous consideration by MSAC

- ☒ The proposed ADAR **will not** contain any changes to the PICO previously considered by MSAC.
- ☐ The proposed ADAR will reflect changes to the PICO as detailed below.

PICO COMPONENT	COMPONENT DESCRIPTION AS CONSIDERED BY MSAC	REVISED COMPONENT DESCRIPTION AND RATIONALE
POPULATION	Test: Patient with newly diagnosed locally advanced or progression to metastatic HR+ /HER2- breast cancer Drug: Patients with AKT pathway altered (<i>PIK3CA</i>, <i>AKT1</i> or <i>PTEN</i>) tumours will be eligible for capivasertib +fulvestrant treatment in 1L or 2L metastatic setting. An integrated co-dependent submission was considered by MSAC and PBAC at its November 2024 meeting. MSAC did not recommend the proposed MBS item for AKT pathway testing. Following a resubmission to PBAC in February 2025, PBAC considered that AKT pathway testing was likely to be useful, but was not mandatory in identifying patients likely to benefit from capivasertib.	No change to original PICO. Request to MSAC to revisit previous decision based on upcoming TGA label change and evaluation of updated data DCO3 from CAPItello-291 study which has prompted the change. The TGA Delegate has recommended restriction of the indication to PIK3CA/AKT1/PTEN pathway genetic mutations.
<PRIOR TEST> (IF APPLICABLE)		
INTERVENTION	Test: A test of tumour tissue for the detection of an AKT pathway altered (<i>PIK3CA</i>, <i>AKT1</i> or <i>PTEN</i>) tumour. Drug: Capivasertib 400 mg (two 200 mg tablets) administered orally twice daily, for 4 days on-	No change to original intervention

	treatment followed by 3 days off-treatment in combination with fulvestrant 500 mg (2 x 250mg/5 ml) intramuscular injections at intervals of 1 month. An additional 500 mg dose is to be given 2 weeks after the initial dose.	
COMPARATOR	Test: No testing Drug: fulvestrant monotherapy	No change to original comparator
OUTCOMES <u>Safety:</u> <u>Effectiveness:</u> <u>Health care system outcomes:</u>	QoL, safety and tolerability PFS, OS, PFS2	No change to original outcomes
SYSTEMATIC REVIEW QUESTIONS – ORIGINAL AS CONSIDERED BY MSAC The submission's therapeutic claim: Capivasertib + Fulvestrant is superior in terms of PFS and inferior but with a manageable safety compared to placebo + Fulvestrant in patients with HR+/HER2- locally advanced (unresectable) or metastatic breast cancer following progression on or after an ET with or without a CDK4/6 inhibitor, who have an AKT pathway alteration (<i>PIK3CA</i> , <i>AKT1</i> , or <i>PTEN</i>). The submission's base case was \$redacted/QALY. Following a resubmission to the PBAC in February 2025, the ICER at \$redacted/QALY was considered cost-effective by the PBAC after a redacted% price reduction to capivasertib. The cost of test was \$redacted and the economic model applied a 18% failure rate to post-analytic failures which adjusted the cost of test to \$redacted.		SYSTEMATIC REVIEW QUESTIONS – CHANGES No change to the therapeutic claim or cost-effectiveness ICER. With the discount to capivasertib proposed in the Feb 2025 PBAC resubmission, the ICER remains cost-effective in all scenarios, including increasing failure rates to 15% as per CAPItello-291. A test cost of \$1,900 proposed in this application (vs \$2,200 in the Feb 2025 resubmission) reduces the ICER further.