MSAC REAPPLICATION TEMPLATE

Reapplication Name:	**Genetic testing to detect estrogen receptor 1 (ESR1) variants in patients with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, to determine eligibility for treatment with PBS subsidised elacestrant**
Previous application number	1782
Name of previous application	Genetic testing to detect estrogen receptor 1 (ESR1) variants in patients with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, to determine eligibility for treatment with PBS subsidised elacestrant

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 Relevance[1] 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. This relates to the medicine (drug).

☒ a service or laboratory requiring accreditation by the National Association of Testing Authorities (NATA)? Please complete the section titled B2: NATA Accreditation. This relates to the test.

☐ 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:	
TGA approved indication(s):	
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).

☐ No. Please explain the differences below, then proceed to the next applicable section (B2: NATA Accreditation; B3: Radiopharmaceuticals; or Other Information)

4. 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

☐ AIMD

☐ Class III

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

☒ No

☐ Yes. Please attach supporting documentation regarding the nature of the exemption, then proceed to the next applicable section (B2: NATA Accreditation; B3: Radiopharmaceuticals; or Other Information).

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

☒ No

☐ Yes.

7. Is the therapeutic good in the process of being considered for inclusion by the TGA?

☐ No.

☒ Yes. Please provide the TGA Application ID and submission date:

Application ID:	Redacted
Submission Date:	Redacted

8. Is the intended purpose in this reapplication the same as the intended purpose in the application for inclusion in the ARTG?

☒ Yes

☐ No. Please explain the differences:

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.

As a company A. Menarini have been collaborating with various pathology groups to prepare for ESR1-mutation testing in Australia: According to the NATA website, the scope of accreditation for genomics liquid biopsy entails the following scope: **Service:** Molecular genetics – detection and characterisation of cell free RNA (cfRNA)/cell free DNA (cfDNA)/cell free TNA (cfTNA) in cancer screening and/or cancer genetic testing. **Product:** o Peter MacCallum Cancer Centre (PMCC), Thermofisher Oncomine Precision GX utilises plasma and o Genomics for Life, Thermofisher Oncomine Breast cfDNA utilises extracted DNA **Determinant:** Nucleic acid analysis for specific variants Both these tests include ESR1-mutation. Redacted

Other Information

Please advise us if there is anything relevant to MSAC's consideration of the reapplication that is not addressed elsewhere in this template. For example, proposed major changes to the ADAR unrelated to matters of concern raised by MSAC; or the health technology is subject to a recall or other regulatory action. You can also list here any additional organisations, experts, or other stakeholders for consultation.

N/A

Table 1: Summary of key matters of concern

COMPONENT	MATTER OF CONCERN	HOW MATTER WILL BE ADDRESSED IN ADAR
Choice of drug comparator	MSAC considered that there is no basis to support ESR1 variant testing, as the PBAC did not recommend the proposed PBS listing of elacestrant. MSAC advised that a resubmission should address the magnitude of clinical benefit with an appropriate comparator and the implementation issues related to the provision of ESR1 testing. MSAC considered the resubmission would need to be an integrated codependent submission and be re-considered by the ESCs. (PSD, p.5, para 2).	**Addressed** A drug comparator of combination treatment with everolimus and exemestane (EVE+EXE) will be nominated in the resubmission.
Delivery of the test	MSAC noted that the Guardant360 assay used in the pivotal trial is not available in Australia and that there are no ctDNA ESR1 tests listed on the Australian Register of Therapeutic Goods (ARTG). MSAC also noted the Pre-Committee Response reported that 2 Australian laboratories are in the process of obtaining accreditation with the National Association of Testing Authorities (NATA) to perform ESR1 testing using ctDNA, but no Australian laboratories are currently accredited for this testing. MSAC therefore queried if the current capacity to offer ESR1 testing is adequate in Australia. (PSD, p.4, para 1).	**Addressed** An update of the status of laboratory accreditation will be provided (see Section B.2 of this form) in Section 1 to provide reassurance that there will be adequate capacity for testing.

MBS Item description	MSAC noted that while the applicant proposed using NGS for ESR1 testing, digital droplet polymerase chain reaction (ddPCR) may be appropriate as an alternative test methodology. Other suitable methodologies may also become available in the future. MSAC noted that while ddPCR has greater sensitivity than NGS and is cheaper (in a high volume laboratory), multiple assays would be required to cover all known ESR1 variants. MSAC considered that, in practice, laboratories would unlikely develop a bespoke ddPCR assay for every variant but rather use an NGS approach. MSAC therefore considered that the MBS item descriptor for ESR1 testing should be method-agnostic. (PSD, p.3, para 5).	**Addressed** The proposed MBS item description will be method agnostic in Section 1.
MBS Item restriction	MSAC noted the ESCs' advice that testing should be restricted to once every 6 months in patients with a previous negative result. However, MSAC considered that testing every 3 months might be a more appropriate timepoint for retesting, noting that this would increase the financial estimates. MSAC advised that there should be no further ESR1 testing following a positive result. (PSD, p.5, para 1)	**Addressed** The proposed MBS item restriction will incorporate this feedback in Section 1.

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: Men and postmenopausal women with ER+/HER2- locally advanced or metastatic breast cancer, who have disease progression following at least one line of endocrine therapy, including a CDK4/6 inhibitor. Drug: Men and postmenopausal women with ER+/HER2- locally advanced or metastatic breast cancer with an activating ESR1 mutation, who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor.	Test: Men and postmenopausal women with ER+/HER2- locally advanced or metastatic breast cancer, who have disease progression following at least one line of endocrine therapy, including a CDK4/6 inhibitor *for ≥12 months* Drug: Men and postmenopausal women with ER+/HER2- locally advanced or metastatic breast cancer with an activating ESR1 mutation, who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor *for ≥12 months* The revised population is within the confirmed PICO population.
COMPARATOR	Test: No testing Drug: Standard of care, consisting of conventional ET (fulvestrant, anastrozole, letrozole, Exemestane).	Test: No change from initial submission Drug: everolimus and exemestane (EVE+EXE)