Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1720 – ^{68}Ga PSMA-11 PET/CT imaging for patients who are candidates for PSMA targeted therapy

Applicant: **Telix Pharmaceuticals Ltd**

Date of MSAC Executive consideration: 25 October 2024
Date of MSAC consideration: 4-5 April 2024

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of ILLUCCIX® Kit (kit for the preparation of gallium-68 (^{68}Ga) labelled prostate-specific membrane antigen (PSMA)-11 injection) for assessing eligibility of patients diagnosed with metastatic castration-resistant prostate cancer (mCRPC) to undertake PSMA targeted therapy was received from Telix Pharmaceuticals Ltd by the Department of Health and Aged Care.

The Commentary noted that the ADAR requested MBS funding for one technology – an investigative test, PSMA positron emission tomography/computed tomography (PSMA PET/CT) and not for the associated therapeutic intervention (PSMA targeted therapy). Although similar to the request in MSAC 1632 and MSAC 1686/MSAC 1686.1 with respect to the test, MSAC 1686/1686.1 also requested MBS funding for the therapeutic intervention.

2. MSAC Executive Outcome 25 October 2024

The MSAC Executive noted the department sought confirmation that Application 1720 had met the conditions made by MSAC at the April 2024 meeting when it deferred the application with a mind to support if it met certain criteria.

Of relevance, MSAC, at its April 2024 meeting, supported application 1686.1 for public funding. This included the listing of two new MBS items for 1) 177Lutetium PSMA imaging scan and therapy(i&t) for treatment of progressive metastatic castrate resistant prostate cancer (mCRPC); and 2) whole body PSMA positron emission tomography/computed tomography (PSMA PET/CT) to identify those eligible for 177Lu PSMA i&t. The MSAC Executive noted MSAC supported MBS item descriptors that are agnostic to the type of 177Lu PSMA therapy and that this advice will be considered by Government. The Department advised that the MBS listing of PSMA PET/CT, to identify suitable patients for therapy, is dependent on the MBS listing of the 177Lu therapy.

The MSAC Executive noted the applicant for 1720 had provided a proposal on 8 October 2024 that addressed the outstanding matters in MSAC's advice following the April 2024 MSAC meeting. The proposal included agreement to the use of an agnostic item descriptor for PSMA PET and a fee of $1,300. The applicant confirmed that its ILLUCCIX® Kit has

received Therapeutic Goods Administration (TGA) approval for "the selection of patients with metastatic prostate cancer in whom lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated." The MSAC Executive noted the TGA approved indication defines the type of 177Lu PSMA therapy. The MSAC Executive noted this indication is narrower than the MSAC supported item for PSMA PET which is agnostic to the type of 177Lu PSMA therapy.

The MSAC Executive confirmed that the applicant's proposal is consistent with the intent of MSAC's advice to support the TGA approved test using an agnostic item descriptor consistent with other PSMA PET MBS items. The MSAC Executive advised the outstanding matters MSAC identified to support public funding had been addressed and that no further consideration by the full MSAC would be required.

MSAC's advice to the Minister April 2024

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC deferred its decision for public funding of the ILLUCCIX® Kit (kit for the preparation of 68Ga labelled PSMA-11 injection) for assessing eligibility of patients diagnosed with mCRPC to undertake PSMA targeted therapy.

MSAC foreshadowed that it was of a mind to support public funding of the proposed test because it accepted PSMA targeted therapy to be cost effective and therefore accepted the clinical need for the test in determining eligibility for PSMA targeted therapy and the evidence of the test's comparative safety and effectiveness. However, MSAC noted the lack of an update on the Therapeutic Goods Administration (TGA) status regarding the approval of the test for the additional indication of "patients who are candidates for PSMA targeted therapy" as per the current application.

MSAC expressed remaining concerns about the high and uncertain incremental cost-effectiveness ratio (ICER). MSAC also had concerns about the lack of evidence supporting superior health outcomes in those identified and treated with PSMA-targeted radioligand therapy using the specific investigative product for 68Ga-PSMA PET/CT compared with other available radiopharmaceutical tracers used for PSMA PET/CT imaging that would be necessary to justify the price premium proposed for the radiotracer specific item. Therefore, MSAC considered that it would be of a mind to support public funding of the proposed test conditional on TGA approval for the additional indication of "patients who are candidates for PSMA targeted therapy" and the amendment of the proposed item descriptor to reflect a lower fee of $1,300 and a radiotracer agnostic item for PSMA-PET.

Consumer summary
This is an application from Telix Pharmaceuticals requesting Medicare Benefits Schedule (MBS) listing of the ILLUCCIX® kit (kit for the preparation of gallium-68 [^{68}Ga]-labelled prostate-specific membrane antigen [PSMA]-11 injection) for assessing the eligibility of patients diagnosed with metastatic castration-resistant prostate cancer to undertake PSMA-targeted therapy.

Consumer summary

Metastatic castration-resistant prostate cancer is a type of advanced prostate cancer that has spread to other parts of the body and has not responded to hormone therapy. In Australia, 3,000 men die each year from this cancer.

Some prostate cancer cells contain a protein called prostate-specific membrane antigen (PSMA), which can be detected by a special type of scan called a positron emission tomography (PET) scan. This application is for a type of PET scan that uses a radioactive chemical called gallium. The gallium is connected to a special molecule (called a ligand) that targets the PSMA receptor on prostate cancer cells. When the ligand attaches to the PSMA receptor, the PET scan can detect the gallium. If a patient's prostate cancers cells are found to have high levels of PSMA, they may be eligible for a therapy that targets the cancer cells that contain PSMA, called PSMA-targeted radionuclide therapy.

This application is for a specific kit for the preparation of the gallium and ligand tracer (called ^{68}Ga-PSMA-11), which is the only PSMA imaging agent that has been approved by the Therapeutic Goods Administration (TGA) although it is currently only approved for a different use to that proposed in this application. However, the tracer has not yet been approved by the TGA for the use of selecting patients for PSMA-targeted therapy, which is the proposed use in this application.

MSAC acknowledged the clinical need for a test that helps select patients who will most benefit from PSMA-targeted therapy given that MSAC had accepted PSMA-targeted therapy as cost effective. However, MSAC noted there were other current PSMA PET MBS items (items 61563 and 61564) with lower fees than those proposed by the applicant. In addition MSAC noted that an item number covering a test for assessing eligibility for PSMA-targeted therapy was included as part of another MSAC application (1686.1) and this item, which did not specify the tracer required, proposed a fee of $1,300, which is also lower than the proposed fee of $1,945 quoted by this application. MSAC considered that there was no evidence provided that showed that the gallium test is better or resulted in better health outcomes than other tracers that would justify a higher fee than $1,300, so the higher fee was not warranted.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC deferred its decision on funding the ILLUCCIX® kit for the preparation of ^{68}Ga-PSMA-11 injection for assessing the eligibility of patients diagnosed with metastatic castration-resistant prostate cancer to undertake PSMA-targeted therapy. MSAC advised that, before it could provide a positive recommendation for public funding, the proposed fee should be lowered to match other similar proposed PSMA PET MBS items, the item descriptor should not name a specific tracer, and the TGA must first approve using the test for selecting patients for PSMA targeted therapy.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from Telix Pharmaceuticals Ltd was requesting Medicare Benefits Schedule (MBS) listing of the ILLUCCIX® kit (kit for the preparation of gallium-68 [^{68}Ga]- PSMA-11 injection) for assessing the eligibility of patients diagnosed with mCRPC to

undertake PSMA-targeted therapy. MSAC noted that the ILLUCCIX® formulation is the only PSMA diagnostic agent approved by the Therapeutic Goods Administration (TGA). MSAC noted that the ADAR stated that an application had been submitted to the TGA for the additional indication of "patients who are candidates for PSMA targeted therapy' which is the precise indication for the proposed MBS listing (see Section 5 Prerequisites to implementation of any funding advice). However, it has not yet been approved by the TGA for this indication.

MSAC recalled it had previously considered PSMA PET/CT for informing the treatment of patients with prostate cancer in two previous applications (MSAC 1632; and MSAC 1686/1686.1).

MSAC noted that the applicant-developed assessment report (ADAR) only requested MBS funding using the radiotracer specific investigative test ^{68}Ga-PSMA PET/CT but not the associated therapeutic intervention (PSMA targeted therapy). This is unlike MSAC applications 1686 and 1686.1 (177 lutetium PSMA imaging scan and therapy [^{177}LuPSMA i&t] for mCRPC]), which also requested MBS funding for the therapeutic intervention (included in the codependent application). MSAC noted this application (1720) proposes a new investigative option (at a higher fee) for identifying those eligible for PSMA-targeted radioligand therapies in a similar population.

MSAC noted that before considering this application, applicant representatives were provided with the opportunity to present at a hearing, At the hearing, applicant representatives highlighted the growing demand and utilisation of PSMA-targeted radioligand therapies, with an analysis of Special Access Scheme (SAS) data provided by the TGA showing that ^{177}Lu-PSMA 617 therapy was requested 455 times in 2021, 420 times in 2022 and 212 times up to 30 June 2023. The representatives also highlighted the growing utilisation of PSMA-targeted therapies at the Peter MacCallum Cancer Centre between 2015 (when Lu-PSMA was first used) and 2022, with ^{177}Lu-PSMA 617 therapy rapidly emerging as standard of care at that centre. MSAC noted that PSMA PET/CT is necessary to assess suitability for PSMA radioligand therapy, which meets a high clinical need for patients with mCRPC. MSAC recalled that an item number covering assessment for suitability for ^{177}Lu-PSMA therapy was included with application 1686.1.

MSAC noted that the applicant in its pre-MSAC response supported removing the "once per lifetime" limitation from the item descriptor, but ESC had concluded that this could only be assessed if there was evidence supporting retreatment. However, MSAC noted that although there are published case series reporting that PSMA retreatment can be effective, and a multicentre controlled trial is about to commence recruitment, there is currently no high-level evidence available supporting retreatment and therefore insufficient evidence to assess the claim for removing the once per lifetime limitation. Nonetheless, MSAC agreed with the applicant that no restriction to the number of services was needed. In addition, MSAC recalled that the proposed investigative item for PSMA PET in application 1686/1686.1 did not include a frequency restriction. MSAC also agreed with the applicant that computed tomography (CT) should be removed from the item descriptor, which would be consistent with other MBS items for PET.

In addition, MSAC also considered that '177 lutetium' should be included in the definition of PSMA therapy in the proposed MBS item.

MSAC considered that, while the ILLUCCIX® kit can be sold to smaller private practices and using the kit makes it much easier and cheaper to manufacture the radiopharmaceutical tracer than previous formulations of ^{68}Ga-PSMA-11 (although it is more expensive per vial), the very short half-life of ^{68}Ga meant that it could not be easily distributed to rural and remote areas, so would likely not address equity of access issues for those patients. MSAC also considered that the high cost per vial meant that purchasing a ^{68}Ga generator was likely a cost-neutral option overall for rural and remote centres even after taking account of the lower costs of manufacture facilitated by the vial.

MSAC noted that the proposed fee of $1,945 was $500–600 higher than that of other current PSMA PET MBS items. This fee was also higher than the fee proposed in codependent application 1686.1. At the hearing, representatives of the applicant provided a rationale for the fee, stating that the cost of the ILLUCCIX® kit is $[redacted], ^{68}Ga is $[redacted], and the PET/CT service is $900. The representatives also stated that the current fee for PSMA PET MBS items is inappropriate and causing financial difficulty for patients in both the public and private settings, as it resulted in an out-of-pocket expense of at least $400. MSAC also noted that there have been no increases in the FDG PET fee since the item was introduced to the MBS. However, MSAC considered that the applicant's justification for the higher fee appeared to be that the ILLUCCIX® product was the only TGA-approved PSMA PET tracer and the relative ease (resulting in a lower cost of manufacture) of making the ILLUCCIX® product. MSAC did not consider these justifications to be sufficient, and noted that evidence was not presented that ^{68}Ga-PSMA-11 PET was more effective than alternatives and demonstrated superiority in health outcomes (as discussed further below). Thus, MSAC considered that a fee of $1,300 as proposed for alternative PSMA PET MBS items in application 1686/1686.1 was appropriate for this application.

MSAC noted that this proposed test could apply to a subset of patients having restaging PSMA PET. However, MBS item 61564 (whole-body PSMA PET for the restaging of recurrent prostate adenocarcinoma, applicable twice per lifetime) will not cover all PET scans that such patients will require. It is likely that these patients would have used up their two PSMA PET CTs for recurrent prostate adenocarcinoma before they have been considered for restaging for treatment response given that they may have received multiple lines of treatment (often over many years). Hence MSAC considered that the test would be meeting a need currently not covered by MBS item 61564.

MSAC noted consultation feedback had been received from two professional organisations, three consumer organisations and eight individuals (five consumers, two consumer support personnel and one medical specialist). Overall, feedback was strongly supportive of the MBS listing of the ILLUCCIX® kit. Disadvantages noted included access to diagnostic facilities, and cost. Other feedback stated that there was no alternative technique currently available to determine which patients are suitable for PSMA-based radionuclide therapy and that current best clinical practice requires a fluorodeoxyglucose (FDG) PET scan also be performed, as any significant PSMA/FDG mismatch was a contraindication to Lu-PSMA therapy. The feedback disagreed that the service be limited to only once per lifetime, instead proposing "once per four-treatment cycle course" and disagreed that the descriptor should refer to a specific branded product. Finally, the feedback noted the significant number of patients with prostate cancer living in rural and remote areas with limited access to medical services (and long travel times), and that providing counselling to patients before they receive the results of imaging, as well as information about community support services, would be beneficial.

MSAC noted that the ADAR provided no new clinical trial data on comparative safety or effectiveness for the diagnostic test. Clinical trial data for PSMA targeted therapy were from the VISION and TheraP trials (both used ^{177}Lu-PSMA 617 products), which were the evidence base for applications 1686/1686.1 so have already been considered by MSAC.

Regarding comparative safety, MSAC recalled that it had previously accepted that PSMA PET/CT (and thus ^{68}Ga-PSMA PET/CT) was adequately safe for assessing individuals with prostate cancer, both for initial staging and recurrence. Moreover, MSAC had previously accepted the comparative safety of PSMA/PET CT (and thus ^{68}Ga-PSMA PET/CT) to determine eligibility for ^{177}Lu PSMA i&t for mCRPC in applications 1686 and 1686.1.

Regarding comparative effectiveness, MSAC noted the main clinical claim made by the ADAR was that, in patients who are candidates for PSMA targeted radioligand therapy, identification via ^{68}Ga-PSMA-11 PET/CT is superior to no ^{68}Ga-PSMA-11 PET/CT. The commentary had considered this reasonable but that the ADAR had not demonstrated the clinical utility of the test, with results from the Re-SPECT[1] study casting doubt on the ability of the test to sufficiently discriminate patients who are likely to respond to PSMA-targeted therapies versus those who are not. MSAC noted the Re-SPECT study, VISION and TheraP trials enrolled patients with mCRPC who were PSMA PET-positive. However, MSAC considered the Re-SPECT trial to be lower-quality evidence than the VISION or TheraP trials (which both used ^{68}Ga-PSMA-11 PET to select patients for Lu-PSMA therapy). so there was indeed higher certainty evidence available for the effectiveness of ^{68}Ga-PSMA-11 PET–directed PSMA targeted therapy.

MSAC also noted the commentary had considered that the ADAR had not provided sufficient evidence to support restricting the radiopharmaceutical to ^{68}Ga as there was no evidence demonstrating the superiority of ^{68}Ga versus other radiotracer specific options, and that restriction to a specific radiopharmaceutical tracer is not consistent with current PSMA PET items on the MBS (items 61563 and 61564) or with that proposed in MSAC applications 1686 and 1686.1. At the hearing, representatives of the applicant stated that the MBS listing should be radiotracer-specific because ^{68}Ga-PSMA-11 is among the most widely used agents for prostate cancer PET/CT imaging, is the only TGA-approved PSMA diagnostic agent in Australia that is specific to the ^{68}Ga tracer (although TGA approval for the indication specific to this application is in process as stated by the ADAR), and was the specific test used in the pivotal trials in the ADAR (VISION and TheraP), so had abundant clinical trial data available. However, noting the agnostic nature of other MBS items for PSMA PET and the overall preference for agnostic MBS items where possible, MSAC considered that the item descriptor should be agnostic to the radiopharmaceutical tracer for PSMA PET.

MSAC also noted that ESC had suggested an additional relevant comparison would be between ^{68}Ga-PSMA-11 PET/CT with subsequent treatment with a PSMA-targeted therapy versus other available radiopharmaceutical tracers used for PSMA PET/CT with subsequent PSMA-targeted therapy. MSAC noted the pre-MSAC response in which the applicant considered that the comparison should not be between the proposed ^{68}Ga tracer and other PSMA PET agents because ILLUCCIX® is the only TGA-approved PSMA test in Australia that is specific to ^{68}Ga, and that, because ^{68}Ga-PSMA-11 PET was the specific test used in the pivotal trials used in the ADAR, the combined intervention was appropriate for the model.

[1] Emmett L, John N, Pathmanandavel S, Counter W, Ayers M, Sharma S et al. (2023). Patient outcomes following a response biomarker-guided approach to treatment using 177Lu-PSMA-I&T in men with metastatic castrate-resistant prostate cancer (Re-SPECT). Ther Adv Med Oncol 15:1–11.

However, MSAC considered that ^{18}F-DCFPyl was an agent that had almost identical imaging biodistribution to ^{68}Ga-PSMA-11 and had been used in some trials, and could therefore serve as a relevant comparator. MSAC also considered another agent, PSMA-1007, but evidence for its use in determining treatment eligibility is lacking, and the maximum standardised uptake value (SUV_{max}) and tumour-to-background cut-off values were yet to be defined.

MSAC noted that the economic evaluation was a cost-utility analysis based on the use of ^{68}Ga-PSMA-11 PET (using the cost of ILLUCCIX®) and Lu-PSMA therapy. A hybrid model (decision tree and a partitioned survival model) was used; extensive similar modelling had already been undertaken and remodelled at least twice for application 1686.1. Although this application does not stipulate a specific therapy agent it assumed that the price of ^{177}Lu PSMA i&t proposed in application 1686/1686.1 could be directly applied to ^{177}Lu-PSMA 617 (considered as a proxy for PSMA targeted therapy) in the economic evaluation. MSAC noted that the ADAR proposed ^{177}Lu-PSMA 617 versus a weighted comparator of 25% cabazitaxel and 75% best supportive care (BSC) (the weighting previously agreed by MSAC to be the most appropriate, and accepted by the applicant in the pre-MSAC response) resulted in an incremental cost-effectiveness ratio (ICER) of $123,611 per quality-adjusted life year (QALY).

MSAC noted that the economic model was most sensitive to the time horizon (decreasing it from 10 years to 5 years increased the ICER by approximately 46%) and the cost of ^{177}Lu-PSMA therapy (assumed cost of ^{177}Lu-PSMA 617 based on cost of ^{177}Lu PSMA i&t in application 1686/1686.1. In the pre-MSAC response, the applicant stated that a time horizon of 5 years was too short as ^{177}Lu-PSMA therapy prolonged overall survival. A 7.5-year time horizon was tested as per application 1686.1 and was found to increase the ICER by 6% (compared to using a 10-year time horizon). The applicant's pre-MSAC response also addressed ESC's concerns about BSC drug costs not being included in the model, stating that these were expected to be minimal, and the costs associated with bone pain treatment had already been included.

Regarding the financial impacts, MSAC noted that the ADAR estimated that approximately 751 patients will undergo a PSMA PET/CT scan in Year 1 and, of these, 676 patients will commence ^{177}Lu-PSMA therapy The ADAR reported the cost to the MBS for PSMA PET/CT to be $1.3 million in Year 1 increasing to $2.8 million in Year 6 while the net financial impact to the MBS for the whole combined test and therapy was estimated to be $20.9 million in Year 1 increasing to $44.8 million in Year 6. MSAC noted the financial estimates were updated in the pre-ESC response.

MSAC deferred its decision on funding ^{68}Ga-PSMA-11 PET for assessing the eligibility of patients diagnosed with mCRPC to undertake PSMA-targeted therapy. MSAC accepted PSMA targeted therapy as cost effective and therefore accepted the clinical need for the test in determining eligibility for PSMA targeted therapy. MSAC advised that, it would be of a mind to support public funding of the proposed test contingent on:

- TGA approval for the additional indication of "patients who are candidates for PSMA-targeted therapy".
- the use of an agnostic item descriptor for PSMA PET, consistent with other PSMA PET MBS items.
- a fee of $1,300, consistent with the other PSMA PET MBS items.

MSAC considered that a higher fee for ^{68}Ga-PSMA-11 PET would need to demonstrate additional value in terms of improved health outcomes in those identified and treated with

PSMA-targeted radioligand therapy using the specific investigative product for ^{68}Ga-PSMA-11 PET/CT compared with other available radiopharmaceutical tracers used for PSMA PET/CT imaging (which would require a resubmission).

4. Background

MSAC has not previously considered ILLUCCIX® testing for the current indication.

However, MSAC has considered PSMA PET/CT in two previous applications, MSAC 1632 and MSAC 1686/1686.1. A summary of those considerations is presented below.

MSAC 1632 (MSAC 1632 July 2021 public summary document [PSD], p1)

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for PSMA PET/CT for informing treatment of patients with prostate cancer. MSAC advised that PSMA PET/CT had at least non-inferior safety and superior effectiveness in terms of superior diagnostic accuracy and clinical utility; in particular, its ability to change management intent compared with conventional imaging in the initial staging and restaging of prostate cancer. In addition, MSAC advised that PSMA PET/CT had acceptable cost-effectiveness and financial impact.

MSAC 1686 (MSAC 1686 July 2022 PSD, pp1-2)

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of 1) ^{177}Lu PSMA i&t therapy for treatment of progressive mCRPC and 2) whole body PSMA PET/CT to identify those eligible for ^{177}Lu PSMA i&t. MSAC acknowledged the high clinical need for this population with advanced disease, and the consumer preference for ^{177}Lu PSMA therapy over its comparators of best supportive care and cabazitaxel. MSAC noted the limitations in the evidence comparing ^{177}Lu PSMA i&t and ^{177}Lu PSMA-617 products, but concluded from the evidence available that these two products are mutually noninferior and thus considered the evidence for ^{177}Lu PSMA-617 to be relevant for ^{177}Lu PSMA i&t. MSAC accepted the high certainty from the evidence that ^{177}Lu PSMA i&t therapy is acceptably safe and effective, but that the incremental cost-effectiveness ratio (ICER; $81,653) was too high and uncertain.

MSAC 1686.1 (MSAC 1686.1 July 2023 PSD, pp1-2)

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC deferred its advice regarding the public funding of 1) ^{177}Lu PSMA i&t therapy for treatment of progressive mCRPC and 2) whole body PSMA PET/CT to identify those eligible for ^{177}Lu PSMA i&t therapy.

MSAC noted the high clinical need for this population with advanced disease. MSAC reconsidered the evidence base and the additional perspectives comparing ^{177}Lu PSMA i&t and ^{177}Lu PSMA-617 products. MSAC noted the limitations in the evidence base but concluded that the two products are mutually noninferior and thus considered the evidence for ^{177}Lu PSMA-617 to be relevant for ^{177}Lu PSMA i&t. Thus, MSAC accepted the evidence that ^{177}Lu PSMA i&t therapy is acceptably safe and effective but continued to have concerns that the incremental cost-effectiveness ratio (ICER; $73,662) was too high and uncertain.

MSAC noted that the proposed two-step approach to treatment was not captured by the structure of the model. MSAC also considered that the financial impact was underestimated.

MSAC deferred its advice and requested that a revised economic evaluation be conducted with the model structure corrected to capture the two-step approach to treatment proposed in the MBS items and reduce the uncertainty created in the model by the patient-level data from different trials in the same model for determination of PFS benefits and costs associated with the intervention. In addition, MSAC requested better justification (or removal) of the selected treatment specific utility weights.

MSAC noted the patent related issues raised during the consultation process. MSAC referred to its Terms of Reference in concluding that patent related matters would require consideration by government prior to the listing of any MBS items as a result of this application (if subsequently supported).

5. Prerequisites to implementation of any funding advice

The ADAR stated that the applicant intended to apply to the TGA in March 2022 for the indication which is the subject of this current application:

> Patients who are candidates for PSMA targeted therapy.

The ADAR stated that TGA approval for patients who are candidates for PSMA targeted therapy which is the subject of this current application is currently in process.

ILLUCCIX® was granted Therapeutic Goods Administration (TGA) approval (ARTG 356332 and ARTG 356333) on 2 of November 2021 for the PET imaging of men with prostate cancer. Specifically:

1. Who are at risk of metastasis and who are suitable for definitive initial therapy.
2. Who have suspected recurrence based on elevated serum Prostate-specific antigen (PSA) level.

There are currently 105 sites throughout Australia with PET units (Australian Government[2]), most of which are in NSW (32), Queensland (27) and Victoria (22).

6. Proposal for public funding

The applicant proposed to create a new MBS item for a radioisotope specific (^{68}Ga)-PSMA PET/CT imaging to determine eligibility for PSMA-targeted therapy (Table 1).

[2] https://www.health.gov.au/topics/diagnostic-imaging/mri-and-pet-locations/PET-Australia#pet-units-in-australian-capital-territory [accessed 28 November 2023]

Table 1 Proposed MBS item descriptor for ^{68}Ga-PSMA PET/CT imaging

Category 5 – DIAGNOSTIC IMAGING SERVICES Group I4 – Nuclear Medicine Imaging Subgroup 2 – PET
MBS XXX Whole body ^{68}Ga prostate-specific membrane antigen (^{68}Ga-PSMA) positron emission tomography (PET)/computed tomography (CT) study, performed for the patient selection for PSMA targeted radioligand therapy. Applicable only once per lifetime Fee: $1,945

Abbreviations: CT, Computed tomography; Ga, Gallium; MBS, Medicare Benefits Schedule; PET, Positron emission tomography; PSMA, Prostate-specific membrane antigen.
Source: ADAR 1720, Table 1-4.

The Commentary noted the following issues that require consideration:

- Specification of the radiopharmaceutical: unlike the current items for PSMA PET/CT on the MBS (items 61563, 61564) and that proposed in the MSAC 1686/1686.1 applications, the item descriptor specifies the radiopharmaceutical, ^{68}Ga. The ADAR provides no evidence to support restricting use to ^{68}Ga (other than this was the radiopharmaceutical used in the two trials used as the evidence base for the ADAR [VISION and TheraP]) or for the radiopharmaceutical to be agnostic (providing evidence that health outcomes would be considered non-inferior regardless of the radiopharmaceutical used).
- Inclusion of CT: The proposed item descriptor refers to both a PET and CT study. This is in contrast to the current MBS items (61563 and 61564) and the proposed item descriptor in MSAC 1686/1686.1 (MSAC 1686.1 July 2023 PSD, Table 5, p9). These new items for PSMA PET [61563 and 61564] do not include reference to CT as CT attenuation item 61505 will generally be claimed with the items (MSAC 1686 July 2022 PSD, p34).
- Description of the eligible population: The proposed item descriptor is not consistent with the description of patients specified in the PICO criteria reported in the ADAR, or with the proposed item descriptor in MSAC 1686/1686.1 (MSAC 1686.1 July 2023 PSD, Table 5, p9), which also better described the patients in the VISION and TheraP trials:

  > Whole body prostate specific membrane antigen (PSMA) positron emission tomography (PET) study, performed for the assessment of suitability for Lutetium 177 PSMA therapy in a patient with metastatic castrate resistant prostate cancer after progressive disease has developed while on at least one taxane chemotherapy and at least one androgen receptor signalling inhibitor.

  Based on the description of the population in the item descriptor, there is also a lack of clarity as to whether those who are candidates for PSMA targeted therapy would also be eligible for PSMA PET/CT under population (b) of MBS item 61564:

  > Whole body prostate-specific membrane antigen PET study performed for the restaging of recurrent prostate adenocarcinoma, for a patient who: (a) has undergone prior locoregional therapy; and (b) is considered suitable for further locoregional therapy to determine appropriate therapeutic pathways and timing of treatment initiation).

  It is also unclear if patients who undergo PSMA PET/CT for staging purposes under MBS item 61564, would undergo another PSMA PET/CT specifically for the purposes of ascertaining whether they are candidates for PSMA targeted therapy (under the proposed item). If a separate scan (for staging vs eligibility) is not required and a generic descriptor is deemed appropriate (i.e., not radiopharmaceutical specific), then an option to expand MBS item 61564 to include determining eligibility for PSMA targeted therapy rather than

creating a new item number may be a possibility. However, should a new item be deemed necessary, restrictions on use with regards to MBS item 61564 will be required.

- Proposed fee: The requested fee of $1945 is greater than the current items for PSMA PET/CT on the MBS (items 61563, 61564) and that proposed in the MSAC 1686/1686.1 applications (MSAC 1686.1 July 2023 PSD, Table 2, p9) of $1300 (or $1400 if CT is included). The rationale provided in the ADAR for the fee is a breakdown of costs and the claim that use of ^{68}Ga, specifically, contributes to the proposed fee.
  The breakdown of costs for the test are presented in Table 2.

Table 2 Cost per ^{68}Ga-PSMA-11 PET/CT imaging

Item	Cost
PSMA-11 Kit (ILLUCCIX®)	$[redacted]
68Ga1	$[redacted]
PET-CT Scan	$900
Other	n/a
MBS Item Total	$1,945

Source: Table 1-3, p38 of the ADAR

[1] A Good Manufacturing Practice (GMP) grade 68Ga generator costs approximately $110,000 and has a useful lifetime of approximately 9 months. During this lifetime, a 68Ga generator can produce approximately [redacted] patient doses per 9 months (i.e., $[redacted]/scan).

The ADAR suggests a fee of $[redacted] per dose for the ILLUCCIX® kit (the Commentary notes that the proposed item descriptor, however, does not specify use of the ILLUCCIX® kit). The ADAR also states that one kit makes up to three individual patient doses; the pre-MSAC response clarified that the nominated $[redacted] fee represents the cost for the entire kit (making three doses) therefore equating to a cost of $[redacted] ($[redacted]/3) per dose.

With respect to claims regarding the use of ^{68}Ga specifically, the MSAC 1686 July 2022 PSD (p8) states that "^{68}Ga or ^{18}F labelled tracers are often used in Australia" already and in fact, the most widely used radiopharmaceutical tracer in PSMA PET/CT imaging for informing treatments of patients with prostate cancer is ^{68}Ga-PSMA-11 (MSAC 1632 July 2021 PSD, p5). Given ^{68}Ga is the most commonly used radiotracer and the ILLUCCIX® kit could be used for MBS items 61563/61564 with a fee of $1300, the Commentary considered further justification for the proposed fee is required. The pre-ESC response argued that the MBS item 61563/61564 fee underestimates the true cost of administering whole body 68Ga prostate-specific membrane antigen (68Ga-PSMA) positron emission tomography (PET).

The Commentary noted that should CT be removed from the item descriptor, the fee should reduce by $100 (the fee associated with MBS item 61505, see above). Alternatively, if CT has been erroneously included in the item descriptor, the total fee for the service would be $2045 (which is the fee applied in the economic evaluation).

Regardless, the greatest permissible gap (GPG) will apply. From 1 November 2023, the GPG is set at $98.70, which means that all out-of-hospital Medicare services which have an MBS fee of $658.35 or more will attract a benefit that is greater than 85% of the MBS fee.
The Commentary also noted that as the proposed test is aimed at assessing eligibility for PSMA targeted therapies, of which none are currently funded on the MBS (or PBS), there is no clinical need for this test at this time (though use of luteium-177 PSMA imaging & therapy (^{177}Lu PSMA i&t) is delivered in some hospitals and is understood to be paid for by patients). There is also uncertainty about the cost of PSMA targeted therapies given none are

currently listed; this is tested in sensitivity analyses. However the pre-ESC response submitted as further evidence for the clinical need of this test that analysis of Special Access Scheme data provided by the TGA showed that ^{177}Lu PSMA 617 was requested for use 455 times in 2021, 420 times in 2022 and 212 times until 30 June 2023.

The pre-ESC response provided an updated item descriptor in response to the Commentary's comments regarding specification of CT and the proposed target population (Table 3).

Table 3 Pre-ESC responses amended MBS item descriptor for ^{68}Ga-PSMA PET/CT imaging

Category 5 – DIAGNOSTIC IMAGING SERVICES Group I4 – Nuclear Medicine Imaging Subgroup 2 – PET
MBS XXX Whole body ^{68}Ga prostate-specific membrane antigen (^{68}Ga-PSMA) positron emission tomography (PET)~~/ computerised tomography (CT)~~ study, performed for the patient selection for PSMA targeted radioligand therapy *in a patient with metastatic castrate resistant prostate cancer after progressive disease has developed while on at least one taxane chemotherapy and at least one androgen receptor signalling inhibitor.* Applicable only once per lifetime Fee: $1,945

Abbreviations: CT, Computed tomography; Ga, Gallium; MBS, Medicare Benefits Schedule; PET, Positron emission tomography; PSMA, Prostate-specific membrane antigen. Proposed additions in italics and proposed deletions as strikethrough.

7. Population

As noted above, there are inconsistencies in the ADAR with respect to the population eligible for the test. The proposed item descriptor suggests the test be used for "patient selection for PSMA targeted radioligand therapy" whilst the PICO criteria specified in the ADAR (and consistent with patients enrolled in the VISION and TheraP trial) defines the population as:

> Patients with progressive or symptomatic metastatic castrate resistant prostate cancer (mCRPC), AND have received:
> - at least one androgen-signalling inhibitor (ASI; abiraterone / enzalutamide / darolutamide via PBS/RPBS), AND
> - at least one line of chemotherapy (docetaxel +/- cabazitaxel via PBS/RPBS).

8. Comparator

The nominated comparator is "No ^{68}Ga-PSMA-11 PET/CT imaging".

The Commentary noted that the comparison provided in the ADAR is one of "No ^{68}Ga-PSMA-11 PET/CT imaging" and subsequent treatment with supportive care or cabazitaxel. The ADAR does not provide a comparison of "No ^{68}Ga-PSMA-11 PET/CT imaging" and subsequent treatment with PSMA targeted therapy. The latter comparison would inform the clinical utility of the proposed test.

The clinical utility of the test may be questionable as 85% and 90% of patients in the VISION and TheraP trials, respectively, met the nominated eligibility criteria for PSMA PET/CT in the respective trials (i.e., a high proportion of patients, thus the requirement for prior testing is not clear).

Additionally, recent data from the Re-SPECT study reported by Emmett (2023[3]) further casts doubt on the ability of PSMA PET/CT to sufficiently discriminate patients who are likely to respond to PSMA targeted therapy and the codependent relationship of PSMA PET/CT with PSMA targeted therapies. In Re-SPECT, all men had mCRPC with a maximum standardised uptake value (SUV_{max}) >15 on PSMA PET at ≥1 site, and SUV_{max} >10 at all measurable sites. Despite these uptake values, among men treated with ^{177}Lu PSMA i&t, 36 of 116 (31%) were considered limited/non-responders.

However, the pre-ESC response submitted that:

- the potential identification of 10-15% of patients as non-eligible through this diagnostic modality was significant fiscal relevance given the substantial expense associated with PSMA targeted therapies.
- the findings of Re-SPECT study should be interpreted with caution as it is a retrospective study and further research in the form of prospective, randomized controlled trials is needed to confirm the effectiveness and generalizability of this approach.

The Commentary considered that of further interest would be a comparison of ^{68}Ga versus other PSMA radiopharmaceutical tracers given the proposed item descriptor specifies the use of ^{68}Ga. Concordance between radiopharmaceuticals was explored in MSAC 1632 where the PSD, pp17-18 explains that "Available concordance studies provide preliminary evidence to suggest ^{18}F-PSMA-1007 and ^{18}F-DCFPyL may be non-inferior to ^{68}Ga-PSMA-11 (Dietlein et al., 2017[4]; Kuten et al., 2020[5]). In fact, Kuten et al (2020) found ^{18}F-PSMA-1007 may detect additional low-grade lesions of limited clinical relevance, while Dietlien et al. (2017) found ^{18}F-DCFPyL to have improved detection rates at PSA levels between 0.5 and 3.5 ng/ml after RP. However, the Commentary considered it was difficult to draw conclusions given a small sample size [n=16] (Kuten et al., 2020) or lack of reference standard validation to differentiate true positive (TP) and false positive (FP) findings (Dietlein et al., 2017)".

9. Summary of public consultation input

Consultation input from was welcomed from two (2) professional organisations, three (3) consumer organisations and eight (8) individuals, of whom five were consumers, two were consumer support personnel and one a medical specialist.

The five (5) organisations that submitted input were:

- Australasian Association of Nuclear Medicine Specialists (AANMS)
- Prostate Cancer Foundation of Australia (PCFA)
- Australian Diagnostic Imaging Association (ADIA)
- High Risk & Advanced Prostate Cancer Support Group Australia and Geelong Prostate Support Group
- Victorian Prostate Cancer Support Groups.

[3] Emmett L, John N, Pathmanandavel S, et al. Patient outcomes following a response biomarker-guided approach to treatment using 177Lu-PSMA-I&T in men with metastatic castrate-resistant prostate cancer (Re-SPECT). Therapeutic Advances in Medical Oncology. 2023;15. doi:10.1177/17588359231156392

[4] Dietlein F, et al. PSA-Stratified Performance of 18F- and 68Ga-PSMA PET in Patients with Biochemical Recurrence of Prostate Cancer. J Nucl Med. 2017 Jun;58(6):947-952. doi: 10.2967/jnumed.116.185538. Epub 2016 Dec 1. PMID: 27908968.

[5] Kuten J, et al. Head-to-Head Comparison of 68Ga-PSMA-11 with 18F-PSMA-1007 PET/CT in Staging Prostate Cancer Using Histopathology and Immunohistochemical Analysis as a Reference Standard. J Nucl Med. 2020 Apr;61(4):527-532. doi: 10.2967/jnumed.119.234187. Epub 2019 Sep 27. PMID: 31562225.

Benefits

- Enable patients with prostate cancer to know whether they will be suitable for their proposed radionuclide therapy
- Greater accuracy and immediacy of results, with patients benefiting from treatment commencing sooner than with the current step-by-step processes for accurate diagnosis
- Potentially increase the number of therapeutic options available for metastatic cancer
- May lead to a significant cost saving if the scan identifies the patients who are unsuitable for LuPSMA and therefore do not proceed with a futile expensive therapy
- Patients receiving adequate and appropriate therapy will have improved quality of life over existing therapies
- Potential for cancers other than prostate cancer to be found using PSMA-PET imaging.

Disadvantages

- Access to the diagnostic facilities
- Cost of the imaging.

Other feedback

There is no alternative technique available to determine whether patients with metastatic prostate cancer are suitable for therapy with radionuclides labelled to PSMA, including Lutetium-177 PSMA LluPSMA), as only the diagnostic PET scans using PSMA can determine whether the known metastatic disease expresses PSMA in sufficient amounts to render them suitable for LuPSMA therapy.

In addition, a FDG PET scan is required as current best clinical practice, as occasionally some or most of the prostate cancer metastases lose the ability to express PSMA but are metabolically “active” and hence visible on FDG PET scans. Any significant PSMA/FDG mis-match is a contra-indication to LuPSMA therapy.

The feedback disagreed that the “only once per lifetime” clause should be included as patients will typically require restaging and may need more than one course of treatment. The wording "once per 4 treatment cycle course" was proposed.

The suggestion was made to specify funding for ^{68}GaPSMA-11 rather than a specific branded product.

Feedback noted that the significant numbers of prostate cancer patients who live in rural or remote areas where access to medical services can be limited, with long travel times for diagnosis and treatment.

Counselling would benefit patients prior to receiving the results of the imaging, along with information about community support services.

10. Characteristics of the evidence base

Table 4 presents a summary of the key features of the included evidence.

Table 4 Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Prognostic evidence (longitudinal accuracy)	2 RCTs and 13 single arm studies.	☐ k=15 n=1,659	High
Change in patient management	2 single ^{177}Lu PSMA-617 arms from 2 RCTs 3 prospective studies (^{177}Lu PSMA-617)	☐ k=5 n=1,455	High
Health outcomes	2 OL RCTs 1) ^{177}Lu PSMA-617 versus cabazitaxel 2) ^{177}Lu PSMA-617 + BSc versus BSc alone	☐ k=2 n=1,031	High

^{177}Lu = ^{177}lutetium; BSc = best supportive care; k = number of studies; n = number of patients; OL = open label; PSMA = prostate specific membrane antigen; RCT = randomised controlled trial; SUV_{max} = maximum standardised uptake value

11. Comparative safety

^{68}Ga-PSMA-11

The ADAR presented safety data of ^{68}Ga-PSMA-11 PET/CT imaging derived exclusively from the VISION trial. No evidence to support the safety of ^{68}Ga-PSMA-11 PET/CT imaging compared to other types of imaging was provided.

There were 3 deaths reported in the study. One subject died from cerebral (subdural) hematoma, the second died from left ventricular dysfunction and the third subject died due to cardiorespiratory arrest. Cardiorespiratory arrest occurred in a patient randomized to the ^{177}Lu-PSMA-617 arm; however, the other two events occurred in patients who were not enrolled. Neither event was deemed related to ^{68}Ga-PSMA-11 administration.

The ADAR surmises that safety data from the VISION study indicate that ^{68}Ga-PSMA-11 PET/CT imaging is safe and well-tolerated in patients with prostate cancer and shows a comparable safety profile to other medical imaging products. Diagnostic radiopharmaceuticals (microdose products with short half-lives) are unlikely to trigger changes in laboratory parameters, vital signs, and/or ECG parameters.

The Commentary acknowledged that safety and efficacy of PSMA PET/CT regardless of the types of radiopharmaceutical tracer was confirmed by MSAC in 1632 Final PSD: “MSAC advised that PSMA PET/CT had at least non-inferior safety and superior effectiveness in terms of superior diagnostic accuracy and clinical utility; in particular, its ability to change management intent compared with conventional imaging in the initial staging and restaging of prostate cancer” (MSAC 1632 July 2021 PSD, p1).

^{177}Lu PSMA-617 versus cabazitaxel

Overall, a lower proportion of patients experienced an adverse event (AE) in the ^{177}Lu PSMA-617 arm compared to the cabazitaxel arm (86.7% vs 92.9%, respectively) in TheraP. Grade 3 and 4 AEs were lower in the ^{177}Lu PSMA-617 arm compared to the cabazitaxel arm (32.7% vs 52.9%, respectively). The safety results over the 3-year follow-up of the TheraP trial showed consistency with the earlier follow-up of the TheraP trial.

^{177}Lu PSMA-617 + best supportive care versus best supportive care alone

A numerically higher proportion of patients experienced an AE in the ^{177}Lu PSMA-617 + best supportive care arm compared to the best supportive care alone arm (98.1% vs 82.9%, respectively) in VISION. Grade 3 and 4 AEs were numerically higher in the ^{177}Lu PSMA-617 + best supportive care arm compared to the best supportive care alone arm (52.7% vs 38.0%, respectively) in VISION. Less than 1.0% of patients experienced an AE that led to death that was considered by the investigators to be related to ^{177}Lu-PSMA-617.

The safety data comparing ^{177}Lu PSMA-617 to cabazitaxel and best supportive care have previously been considered by MSAC in its consideration of MSAC 1686 in July 2022 (discussed further in Section 10 below under 'Clinical claim').

The ADAR provided no information on any potential, specific safety issues related to excretion of radioactive material post infusion for patients, family members or the broader environment for either ^{68}Ga or PSMA targeted therapies.

12. Comparative effectiveness

Longitudinal accuracy

A total of 15 studies met the inclusion criteria for assessing the test accuracy of ILLUCCIX® imaging in determining response assessment of PSMA radioligand as a prognostic indicator of future outcomes. The ADAR surmises that the evidence strongly supports the use of ^{68}Ga-PSMA-11 PET/CT imaging for the selection of patients prior to PSMA radioligand therapy and aid in the early and accurate assessment of response to therapy.

The Commentary considers that the 15 studies presented in the ADAR were selected based only on the use of ^{68}Ga -PSMA-11. Only two of these studies are randomised controlled trials (VISION and TheraP). The participants from VISION and TheraP were tested only with ^{68}Ga -PSMA-11 for PSMA-positive status and then randomised to PSMA therapy and standard care (VISION) or cabazitaxel (TheraP). As a result, the studies described health outcomes only in PSMA-positive patients with mCPRC treated with PSMA therapy or standard care/cabazitaxel. No randomisation was performed with respect to other radiopharmaceutical tracers or conventional imaging (CVI) to compare with ^{68}Ga-PSMA-11. As a result, there is no evidence to compare health outcomes in mCRPC patients tested with ^{68}Ga -PSMA-11 PSMA PET imaging with mCRPC patients tested with CVI or with other radiopharmaceutical tracer for PSMA PET imaging.

As discussed previously, the Re-SPECT study also informs the longitudinal accuracy and was not one of the 15 studies identified by the ADAR. Given 31% of patients enrolled in Re-SPECT failed to respond to treatment, it is possible that the PSMA PET/CT test, or the nominated eligibility criteria, may not have been sufficiently discriminatory for identifying a population who are likely to respond. This, taken together with the fact that 90% of patients are considered to meet this eligibility criteria for treatment (based on TheraP), also calls into question the codependent relationship of test (PSMA PET/CT) with treatment.

Change in patient management

The ADAR approached the assessment of change in management by assessing the proportion of patients who met eligibility criteria for various studies, according to SUV_{max} thresholds,

see Table 4. The number ineligible for ^{177}Lu PSMA-617 in the studies were similar, however, inexplicably, a numerically greater proportion of patients were deemed eligible in TheraP (90%) despite more stringent PSMA PET/CT threshold criteria (SUV_{max} ≥20 at disease site and ≥10 at all sites of measurable disease) compared with 87.7%-89.9% at SUV_{max} ≥5, 83.7% at SUV_{max} ≥10 and 87.0% at SUV_{max} ≥15. The reason for this is unclear but could potentially be due to unobserved differences in the cohorts of patients from whom those enrolled were derived or from differences in 'reading' and interpreting the scans. These data have previously been considered by MSAC in its consideration of MSAC 1686 in July 2022.

Table 5 Comparison of change in management, by SUV_{max} threshold adopted

	SUV_{max} ≥5 [a]		**SUV_{max} ≥10** [b]	**SUV_{max} ≥15**	**SUV_{max} ≥20**
	Emmett 2019 N=18	**VISION N=1003**	**Hofman et al. (2018) N=43**	**LuPIN N=100**	**TheraP N=291**
Patients scanned, no.	18 (100)	1003 (100)	43 (100)	100 (100)	291 (100)
Patients excluded					
Inadequate PSMA intensity, n (%)	2 (11.1)	123 (12.3)	7 (16.3)	13 (13.0)	29 (10.0)
FDG/PSMA mismatch, n (%)	0	NA		13 (13.0)	51 (17.5)
Other	2 (0.1) [c]	8 (0.8) [d]	6 (13.4) [e]	18 (18.0) [f]	11 (3.8) [g]
^{177}Lu PSMA-617 therapy eligible, n (%)	14 (77.8)	831 (82.9)	30 (69.8)	56 (56.0)	200 (68.7)

[a] SUV_{max} ≥ liver parenchyma, approximately equivalent to SUV_{max} ≥5
[b] SUV_{max} 1.5 x liver parenchyma, approximately equivalent to SUV_{max} ≥10
[c] 4 patients were ineligible for Lu PSMA therapy. Of the 4 men excluded 2 (11%) of 18 had inadequate PSMA intensity and 2 (11%) had inadequate marrow function
[d] 3 patients had progressive disease, 2 had an adverse event, 2 died and 1 withdrew consent
[e] Excluded for reasons based on exclusion criteria in the trial
[f] Scan fails were due to clinical deterioration (6%), concurrent illness (3%), low haemoglobin (7%) or personal reasons (2%)
[g] Reasons for 'other' were not reported
Abbreviations: ^{177}Lu PSMA-617, ^{177}lutetium prostate-specific membrane antigen 617; FDG, fluorodeoxyglucose; NA, not applicable; PSMA, prostate-specific membrane antigen; SUV_{max}, maximum standardised uptake value
Source: Section 2B.3 of the ADAR

The Commentary noted that results from the Re-SPECT study (Emmett 2023) indicated 31% of patients were considered limited/non-responders, despite meeting the eligibility criteria for the study.

Health outcomes

Two open-label, randomised trials formed the evidentiary basis for health outcomes of the ADAR:

- TheraP; compared ^{177}Lu PSMA-617 (n=99) versus cabazitaxel (n=101) in patients with an SUV_{max} of at least 20 at a site of disease and greater than 10 at all other measurable sites of metastatic disease (as per ^{68}Ga PSMA-11 PET/CT), **AND** no sites of metastatic disease with discordant 2-[^{18}F] FDG-positive (FDG PET/CT) and PSMA-negative findings; and
- VISION; compared ^{177}Lu PSMA-617 + best supportive care (BSC; n=551) versus BSC alone (n=280) in patients with ^{68}Ga PSMA-11 (PET/CT) uptake greater than that of liver parenchyma (approximately SUV_{max} threshold of 5 (IQR 4-7)) in one or more metastatic lesions of any size in any organ system.

The results of the trials are presented in Table 5. Kaplan-Meier (KM) curves for OS in VISION and TheraP; and PFS in TheraP and VISION are presented in Figure 1, Figure 2, Figure 3 and Figure 4, respectively. These data have previously been considered by MSAC in its consideration of MSAC 1686 in July 2022 (discussed further below under 'Clinical claim').

Table 6 Summary of ^{177}Lu PSMA-617 efficacy

	TheraP		VISION	
	^{177}Lu PSMA-617	**Cabazitaxel**	**^{177}Lu PSMA-617 + BSC**	**BSC**
Median follow-up (months)	36.0	36.0	20.9	20.9
Response rate (PSA50)				
N	NR	NR	385	196
Events, n (%)	NR	NR	177 (46)	14 (7)
RD (95% CI)	-		**39% (33%, 45%) ***	
p-value	-		**<0.00001 ***	
Overall/objective response (CR+PR)				
N	NR	NR	319*	120*
Events, n (%)	NR	NR	95 (30)	2 (2)
RD (95% CI)	-		**28% (23%, 34%)** [5]	
p-value	-		**<0.00001** [5]	
Overall survival				
N	99	101	551	280
Events, n (%)	77 (77.8)	70 (69.3)	343 (62)	187 (67)
OS (95% CI), months[6]	19.1 (NR)	19.6 (NR)	15.3	11.3
HR (95% CI)	0.97 (0.70, 1.4)		**0.62 (0.52, 0.74)**	
p-value	0.99		**<0.001**	
Progression-free survival				
N	99	101	385	196
Events, n (%)	NR	NR	254 (66)[2]	93 (47)[2]
PFS (95% CI), months[6]	7.1 (NR)	5.0 (NR)	8.7	3.4
HR (95% CI)	**0.62 (0.45, 0.85)**		**0.40 (0.29, 0.57)[3]**	
p-value	**0.0028**		**<0.001**	

Bold indicates statistically significant difference

***** in patients with evaluable disease at baseline (Patients with at least one target lesion or at least one non-target lesion)

[1] in patients with measurable disease by RECIST criteria at baseline

[2] Imaging-based progression-free survival

[3] 99.2% CI

[4] Radiographic or PSA progression-free survival

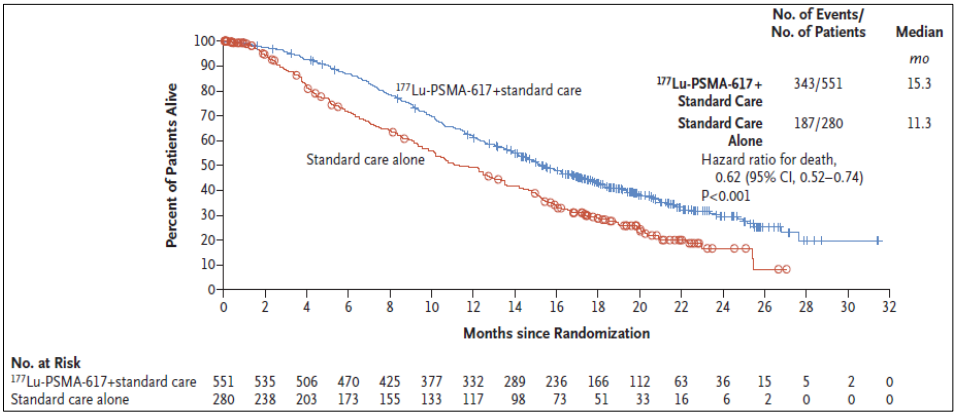
[5] Calculated post-hoc using Review Manager 5.4.1 (Mantel-Haenszel, random effects)

[6] Restricted mean survival in TheraP, median in VISION

Abbreviations: ADAR, applicant developed assessment report; BSc, best supportive care; CR, complete response; HR, hazard ratio; ^{177}Lu, lutetium-177; NR, not reported; PR, partial response; PSA50, prostate-specific antigen reduction of ≥50% from baseline; PSMA, prostate-specific membrane antigen; RECIST, Response Evaluation Criteria in Solid Tumours; RD, risk difference

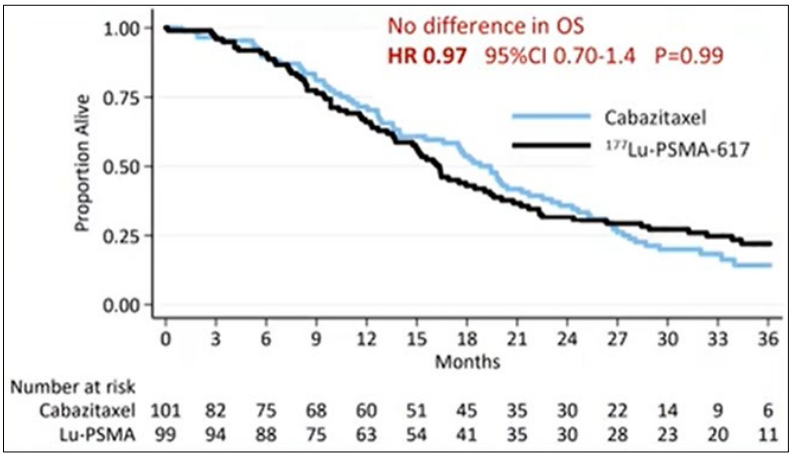
Source: Section 2B.4 of the ADAR

Figure 1 Overall survival in the VISION trial



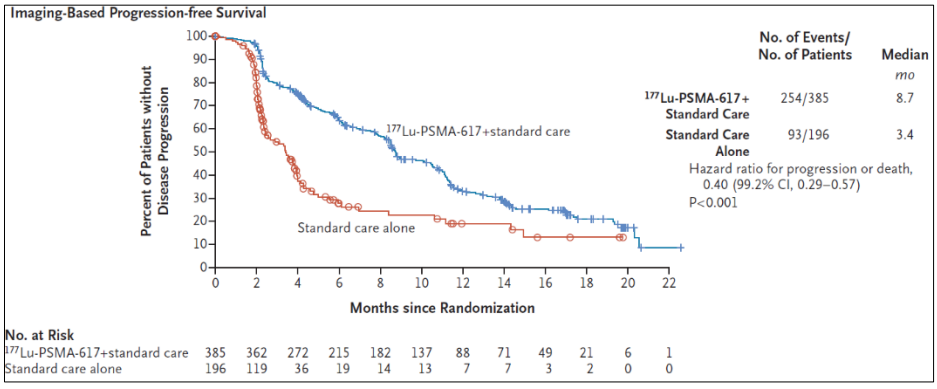
Source: Figure 2-3, p72 of the ADAR
CI, confidence interval; ^{177}Lu-PSMA-617, 177 Lutetium prostate-specific membrane antigen 617; mo, months

Figure 2 Overall survival in TheraP at median follow-up 36 months (ITT)



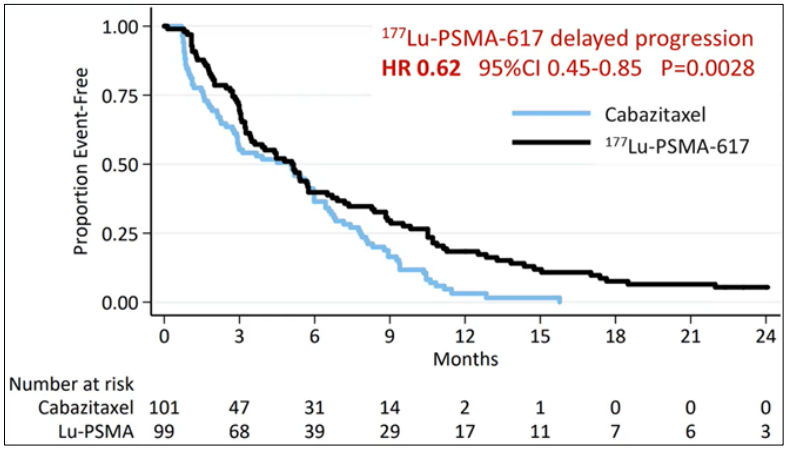
Source: Figure 2-9, p80 of the ADAR
CI, confidence interval; HR, hazard ratio; ^{177}Lu-PSMA-617, 177 Lutetium prostate-specific membrane antigen 617; OS, overall survival

Figure 3 Image-based PFS in VISION trial, rPFS population



Source: Figure 2-4, p72 of the ADAR
CI, confidence interval; ^{177}Lu-PSMA-617, 177 Lutetium prostate-specific membrane antigen 617; mo, months, PFS, progression-free survival; rPFS, radiographic progression-free survival

Figure 4 Image-based PFS in TheraP trial, rPFS population



Source: Figure 2-10, p81 of the ADAR
CI, confidence interval; HR, hazard ratio; ^{177}Lu-PSMA-617, 177 Lutetium prostate-specific membrane antigen 617; mo, months, PFS, progression-free survival; rPFS, radiographic progression-free survival

Across both TheraP and VISION, treatment with ^{177}Lu PSMA-617 was associated with statistically significantly prolonged PFS and overall/objective response rate compared to cabazitaxel and BSC. In VISION, treatment with ^{177}Lu PSMA-617 was also associated with a statistically significant OS advantage (HR=0.62 [95% CI: 0.52, 0.74]; p<0.001) when compared with BSC.

Clinical claim

The ADAR made the following clinical claims:

- In patients who are candidates for PSMA targeted therapy after identification via ^{68}Ga-PSMA-11 PET/CT imaging is superior to no ^{68}Ga-PSMA-11 PET/CT imaging in terms of analytical, clinical validity and clinical utility. The Commentary considered that this has not explicitly been demonstrated, although is likely reasonable. However, the ADAR has not:
  (i) demonstrated the clinical utility of the test, with results from the Re-SPECT study casting doubt on the ability of the test (or at least the nominated thresholds) to sufficiently discriminate patients who are likely to respond to PSMA targeted therapies versus those who are not; and
  (ii) provided sufficient evidence to support restricting the radiopharmaceutical to ^{68}Ga via demonstrating superiority versus other options. Restriction to a single radiopharmaceutical is not consistent with PSMA PET/CT on the MBS (items 61563, 61564) and that proposed in the MSAC 1686/1686.1 application.

- ^{68}Ga-PSMA-11 PET/CT and ^{177}Lu-PSMA-617 results in superior effectiveness compared with cabazitaxel among patients with mCRPC who have an SUV_{max} ≥20 at the disease site and >10 at all measurable sites of metastatic disease with no with PSMA-negative/FDG-positive discordant disease. The Commentary noted this has been accepted by MSAC for outcomes other than OS. MSAC considered that ^{177}Lu PSMA-617 (and thus ^{177}Lu PSMA i&t) is superior for PSA response, overall response rate, PFS, and several quality of life domains and patient reported outcomes (e.g. pain scores) compared with cabazitaxel; MSAC considered that ^{177}Lu PSMA-617 (and thus ^{177}Lu PSMA i&t) has similar OS at three years compared with cabazitaxel (MSAC 1686 July 2022 PSD, p5).

- ^{68}Ga-PSMA-11 PET/CT and ^{177}Lu-PSMA-617 results in superior effectiveness compared with best supportive care. The Commentary noted this has been accepted by MSAC. MSAC considered that ^{177}Lu PSMA-617 (and thus ^{177}Lu PSMA i&t) is superior for PSA response, overall response rate, PFS, and several quality of life domains and patient reported outcomes (e.g. pain scores) compared with best supportive care; MSAC also considered that ^{177}Lu PSMA-617 (and thus ^{177}Lu PSMA i&t) is superior to best supportive care for median OS (MSAC 1686 July 2022 PSD, p5).

- ^{68}Ga-PSMA-11 PET/CT and ^{177}Lu-PSMA-617 results in superior safety compared with cabazitaxel among patients with SUV_{max} uptake greater than that of liver parenchyma in one or more metastatic lesions of any size in any organ system. The Commentary noted that MSAC considered that the different short-term side-effect profiles of ^{177}Lu PSMA-617 and cabazitaxel made direct comparison difficult (e.g. diarrhoea is worse with cabazitaxel) but that the safety of ^{177}Lu PSMA-617 (and thus ^{177}Lu PSMA i&t) is at least noninferior (and likely superior as claimed) to cabazitaxel (MSAC 1686 July 2022 PSD, p5).

- ^{68}Ga-PSMA-11 PET/CT and ^{177}Lu-PSMA-617 has an inferior safety compared with best supportive care. The safety profile was however manageable compared to the comparator arm. The Commentary noted MSAC considered that ^{177}Lu PSMA-617 (and thus ^{177}Lu PSMA i&t) is inferior in safety compared with best supportive care, as there were more short-term AEs for ^{177}Lu PSMA-617 in the [VISION] trial (MSAC 1686 July 2022 PSD, p5).

13. Economic evaluation

A cost-utility analysis was performed using a hybrid model approach which included a decision tree and partitioned survival model (PSM) component. The decision tree captures the proportion of patients who receive ^{68}Ga-PSMA-11 PET/CT imaging and are detected positive for at least one PSMA metastatic and no PSMA negative lesions who then become eligible (90%) to receive ^{177}Lu-PSMA-617 therapy and enter the partitioned survival model.

Two models were generated – one using data from VISION (Sartor et al., 2021) and the other using data from TheraP (Hofman et al., 2021). The base case was generated using a weighted comparator of 75% cabazitaxel (based on the TheraP model) and 25% BSC (based on the VISION model). The Commentary noted that the MSAC 1686 July 2022 PSD (p6) indicates MSAC considered a comparator split of 75% best supportive care and 25% cabazitaxel to be appropriate. The models utilised the Kaplan-Meier curves for each individual arm of the trials, which were also all independently extrapolated using parametric curves. The parametric functions applied from when 10% of patients remained 'at risk' and continued to a 10-year time horizon; the Commentary considered that the time horizon was excessive. In its consideration of MSAC 1686, ESC considered that a time horizon of 5–7 years was more reasonable for the base case results of the model (MSAC 1686 July 2022 PSD, p38). The MSAC 1686.1 ADAR utilised a 7.5 year time horizon. While agreeing with the MSAC's preference for a 5-year horizon, ESC noted that in practice both horizons could be taken into consideration (MSAC 1686.1 July 2023 PSD, p27).

The key components of the base case model presented in the ADAR is summarised in Table 7. Many of the assumptions (comparator split) and inputs (cost of PSMA targeted therapies and utilities) were based on MSAC 1686.

Table 7 Key components of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	Patients with progressive or symptomatic mCRPC
Comparator	Cabazitaxel BSC Weighted comparator of 75% cabazitaxel and 25% BSC.
Type(s) of analysis	Cost-utility analysis
Outcomes	• QALYs • LYs
Time horizon	10 years in base-case
Computational method	Hybrid model (Decision tree + Partitioned survival model)
Health states	Partition survival model has following health states: • Progression free survival • Progressed disease • Death
Utilities	Progression-free survival: 0.74; Progressed disease: 0.59.
Cycle length	1 week
Transition probabilities	• Health state allocation over time determined by PFS and OS data • PFS and OS data for ^{177}Lu-PSMA-617 were sourced from VISION[1] and TheraP[2] • PFS and OS data for cabazitaxel were sourced from TheraP[2] • PFS and OS data for BSC were sourced from VISION[1]
Discount rate	5% for both costs and outcomes
Software	Microsoft Excel 2016

Source: Table 3-1, p90 of the ADAR

Patients enter the model in the PFS state. In each cycle (weekly), patients can either remain in the PFS health state, or transition to the PD or death health state. Patients who have progressed can remain in the PD state or transition to the death state but never go back to the PFS state. All patients eventually enter the death state. Costs relevant to PSMA PET/CT testing, ^{177}Lu PSMA and cabazitaxel were appropriately included, as well as costs for treating Grade 3 or 4 adverse events. The total cost of ^{177}Lu PSMA was assumed to be $8,000, as per MSAC 1686, however the cost of ^{177}Lu PSMA was assumed to be $6,000 and administration $2,000, compared with $5,500 and $2,500 in the MSAC 1686 ADAR (MSAC 1686 July 2022 PSD, p35). Further, some assumptions regarding adverse event (AE) costs and AE disutilities favoured the intervention but these had negligible impacts on the ICER. BSC drug costs were also assumed to be zero (offset in both arms) but there is a possibility that BSC drug costs were higher in the intervention arm. It is also notable that no costs associated with treatment of bone pain such as opioid use, ^{89}strontium (palliative isotope) and local radiotherapy were included.

The model assumes that only patients remaining progression-free will continue with therapy, up to a maximum of 6 cycles. The recent MSAC 1686.1 ADAR proposed splitting treatment, for up to 6 cycles in total, into initial (2 cycles) and continuing treatment (up to 4 cycles). For continuing treatment, only those who have not developed disease progression while receiving ^{177}Lu PSMA i&t for this condition are eligible. The implications of this regimen have not and could not be explored.

The results of the modelled economic evaluations are below.

Table 8 Summary of Base Case Results (discounted): ^{177}Lu-PSMA-617 vs. Cabazitaxel (TheraP)

Parameters	TheraP: ^{177}Lu-PSMA-617	Cabazitaxel	Incremental Outcome	ICER
Total cost	$41,030	$11,362	$29,668	
LYs	1.906	1.707	0.199	$149,023
QALYs	1.220	1.077	0.143	$207,526

^{177}Lu-PSMA-617, ^{177}Lutetium Prostate-specific membrane antigen; LY, life-year; ICER: incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
Source: Table 3-39, p130 of the ADAR

Table 9 Summary of Base Case Results (discounted): ^{177}Lu-PSMA-617 vs. BSC (VISION)

Parameters	VISION: ^{177}Lu-PSMA-617	BSC	Incremental Outcome	ICER
Total cost	$44,516	$6,184	$38,332	
LYs	1.724	1.292	0.432	$88,823
QALYs	1.165	0.822	0.342	$111,934

^{177}Lu-PSMA-617, ^{177}Lutetium Prostate-specific membrane antigen; BSc, Best supportive care; LY, life-year; ICER: incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
Source: Table 3-40, p130 of the ADAR

Table 10 Summary of Base Case Results (discounted): ^{177}Lu-PSMA-617 vs. weighted comparator (75% cabazitaxel : 25% BSC)

Parameters	^{177}Lu-PSMA-617	75% cabazitaxel : 25% BSC	Incremental Outcome	ICER
Total cost	$41,902	$10,067	$31,834	
LYs	1.861	1.603	0.257	$123,771
QALYs	1.206	1.013	0.193	$165,086

^{177}Lu-PSMA-617, ^{177}Lutetium Prostate-specific membrane antigen; LY, life-year; ICER: incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
Source: Table 3-41, p130 of the ADAR

The base case ICER was considered to be high at $165,086 with an assumed comparator of 75% cabazitaxel : 25% BSC. An ICER of $123,611 assuming a comparator of 25% cabazitaxel : 75% BSC (considered appropriated by MSAC (MSAC 1686 July 2022 PSD, p. 6)) was similarly considered to be high.

It is not clear that the economic evaluation is capturing the right comparison as the ICER is derived from a comparison of PSMA PET/CT with subsequent treatment with a PSMA targeted therapy versus no PSMA PET/CT and treatment with BSC or cabazitaxel. Given the ADAR is requesting MBS listing of the PSMA PET/CT test only, a more appropriate comparison may be one of PSMA PET/CT with subsequent treatment with a PSMA targeted therapy versus no PSMA PET/CT with subsequent treatment with a PSMA targeted therapy, to capture the benefit of the test itself, noting that no such evidence exists.

Sensitivity and scenario analyses were conducted by the ADAR and for the Commentary (in shaded cells), see Table 11.

Table 11 Sensitivity analyses conducted by the ADAR and for the Commentary (shaded cells)

Base-case setting	Scenario setting	Incremental		ICER	% change in ICER
		Costs	QALYs		
Base-case		**$31,834**	**0.193**	**$165,086**	
Discount rate: 5% per annum	No discounting	$32,328	0.237	$136,434	-17%
	3.5% discounting	$31,973	0.205	$156,238	-5%
Time horizon: 10 years	Time horizon: 5 years	$31,492	0.130	$241,771	46%
	Time horizon: 7 years	$31,701	0.169	$188,115	14%
Cost of ^{177}Lu-PSMA: $6,000	$4,882	$27,539	0.193	$142,687	-14%
	$7,232	$36,623	0.193	$189,759	15%
Cost of ^{177}Lu-PSMA admin: $2,000	$1,627	$30,421	0.193	$157,620	-5%
	$2,411	$33,449	0.193	$173,310	5%
Cabazitaxel drug cost: $299	$243	$32,085	0.193	$166,245	1%
	$361	$31,615	0.193	$163,809	-1%
^{177}Lu-PSMA-617 (VISION) PFS extrapolation: K-M + Parametric fitting (adj.) using Log-normal distribution. ^{177}Lu-PSMA-617 (VISION) OS extrapolation: K-M + Parametric fitting using log-logistic distribution.	^{177}Lu-PSMA-617 (VISION) PFS extrapolation: K-M + Parametric fitting (adj.) using Generalised Gamma distribution. ^{177}Lu-PSMA-617 (VISION) OS extrapolation: K-M + Parametric fitting using Generalised Gamma distribution. (second best fit based on AIC/BIC value)	$31,745	0.172	$184,405	12%
^{177}Lu-PSMA-617 (TheraP) PFS extrapolation: K-M + Parametric fitting (adj.) using Log-normal distribution. ^{177}Lu-PSMA-617 (TheraP) OS extrapolation: K-M + Parametric fitting using log-normal distribution.	^{177}Lu-PSMA-617 (TheraP) PFS extrapolation: K-M + Parametric fitting (adj.) using Generalised Gamma distribution. ^{177}Lu-PSMA-617 (TheraP) OS extrapolation: K-M + Parametric fitting using Generalised Gamma distribution. (second best fit based on AIC/BIC value)	$31,999	0.240	$133,082	-19%
Cabazitaxel (TheraP) PFS extrapolation: K-M + Parametric fitting (adj.) using Log-normal distribution. Cabazitaxel (TheraP) OS extrapolation: K-M + Parametric fitting using Gamma distribution.	Cabazitaxel (TheraP) PFS extrapolation: K-M + Parametric fitting (adj.) using Gamma distribution. Cabazitaxel (TheraP) OS extrapolation: K-M + Parametric fitting using log-logistic distribution. (second best fit based on AIC/BIC value)	$31,592	0.138	$229,406	39%
BSC (VISION) PFS extrapolation: K-M + Parametric fitting (adj.) using Log-normal distribution. BSC (VISION) OS extrapolation: K-M + Parametric fitting using log-normal distribution.	BSC (VISION) PFS extrapolation: K-M + Parametric fitting (adj.) using Generalised Gamma. BSC (VISION) OS extrapolation: K-M + Parametric fitting using Generalised Gamma	$31,862	0.199	$160,489	-3%

Base-case setting	Scenario setting	Incremental		ICER	% change in ICER
		Costs	QALYs		
	distribution. (second best fit based on AIC/BIC value)				
Source for utility values: - MSAC 1686 PSD: PFS=0.74, PD=0.59	Lloyd A.J. et al., 2015 (EQ-5D-5L): PFS=0.83, PD=0.625	$31,834	0.217	$146,561	-11%
	Lloyd A.J. et al., 2015 (EQ-5D-5L): PFS=0.69 [Pop 3]; PD=0.59	$31,834	0.179	$177,429	+7%
	Lloyd A.J. et al., 2015 (EQ-5D-5L): PFS=0.70 [Pop 4]; PD=0.59	$31,834	0.182	$175,245	+6%
	Lloyd A.J. et al., 2015 (EORTC-8D): PFS=0.856; PD=0.697	$31,834	0.223	$142,837	-13%
	Lloyd A.J. et al., 2015 (EORTC-8D): PFS=0.750 [Pop 3]; PD=0.59	$31,834	0.196	$162,727	-1.5%
	Lloyd A.J. et al., 2015 (EORTC-8D): PFS=0.753 [Pop 4]; PD=0.59	$31,834	0.196	$162,033	-2%
Proportion treated with cabazitaxel of 25%	ADAR 1686.1	$36,166	0.293	$123,611	-25%

Source: Table 3-43, pp134-135 and Figure 3-21, p137 of the ADAR and conducted during the evaluation (shaded cells)

The results show that the model is most sensitive to the following:

- Decreasing the time horizon to 5 years increased the ICER by approximately 46%.
- Cost of ^{177}Lu-PSMA therapy, reducing or increasing the ICER by about 15%.
- Decreasing the discount rate to 3.5% and 0% reduced the ICER by approximately 5% and 17%, respectively.
- PFS and OS extrapolation in cabazitaxel (TheraP): use of second-best fit curves (Gamma for PFS, and Log-logistic for OS) increased the ICER by approximately 39%.
- PFS and OS extrapolation in ^{177}Lu-PSMA-617 (TheraP): use of second-best fit curves (Generalized Gamma for PFS, and Generalized Gamma for OS) increased the ICER by approximately 19%.
- Utilising alternate utility values decreased the ICER by approximately 13% and 11% using EORTC-8D and EQ-5D-5L instruments, respectively. The Commentary noted that Lloyd 2015 described 4 types of participants with mCRPC:
  1. Asymptomatic or mildly symptomatic after failure of ADT, before receiving any chemotherapy (i.e., in whom chemotherapy was not yet clinically indicated) (n=50).
  2. Symptomatic after failure of ADT, before receiving any chemotherapy (i.e., chemotherapy clinically indicated but not started) (n=50).
  3. After failure of ADT, currently receiving chemotherapy (n=17).
  4. After failure of ADT, post chemotherapy (n=46).

The sensitivity analyses presented in the ADAR utilised utilities relevant to Populations 1 and 2 which may be misleading as patients in Populations 3 and 4 are considered to be most reflective of the proposed population. Analyses using Population 3 and 4 utilities for PFS were conducted during the evaluation and these resulted in either smaller reductions in the ICER (1.5% and 2% using the EORTC-8D instrument) or increases (6% and 7% using the EQ-5D-5L instrument).

- Adjusting the comparator split to be cabazitaxel 25% and BSC 75% decreased the ICER by 25%. Although there was an increase in the incremental costs, incremental QALY increased more.

14. Financial/budgetary impacts

The ADAR presented an epidemiological approach to model the financial impact of ^{68}Ga-PSMA-11 PET/CT imaging and ^{177}Lu-PSMA-617 therapy on MBS.

This ADAR is based on the MSAC 1686 July 2022 PSD and relies on the eligible population numbers and many of the assumptions reported in this PSD, although not all.

The assumptions used to inform their model are:

1) No change in the eligible population estimates that applied in MSAC 1686.
2) The cost of the PSMA therapy is the same, $8,000; costs of $6,509 ($4,882+$1,627, see Table 10) and $9,643 ($7,232+$2,411, see Table 10) or $6,410.30 and $9,544.30, respectively with a greatest permissible gap (GPG) of $98.70 applied are tested in sensitivity analyses conducted for the Commentary.
3) Assume the number of PSMA treatment cycles is 4.17 for eligible patients.
4) Treatment cycles for cabazitaxel are 7.32.

The changes to the assumptions that applied are:

- The ADAR assumes an uptake in the first year for therapy of 25%, increasing by 15% each year to 50.3% by Year 6. Evidence to support this assumption, aside from comments in MSAC 1686 July 2022 PSD that the assumption of 11.5% uptake, in Year 1 and a 11.5% increase each year, was too low, was not presented. This assumption is considered to be reasonable by the Commentary because it assumes that at least half of eligible patients will have access to this treatment by Year 6.

- The proportion of patients that are assumed to have subsequent therapy after randomisation is 14.9%, for patients who are allocated to PSMA targeted therapy, cabazitaxel and BSC. The ADAR adjusts the population for whether they receive cabazitaxel or docetaxel as subsequent treatment. However, this proportion is only applied to patients who are assumed to have progressed, which results in different proportions receiving subsequent treatment across the arms. Although it is implied that patients who have progressed would receive subsequent therapy, the evidence used for this proportion [Sartor 2021], only reports that 14.9% of the ITT population received subsequent treatment.

- The ADAR reports results based on a split of 75% receiving cabazitaxel and 25% receiving BSC in the comparator arm. This is adjusted for in the results by the

Commentary, as the MSAC 1686 July 2022 PSD noted that due to its toxicity cabazitaxel use is lower at 25%.

- The ADAR applies different assumptions about the number of PSMA targeted therapy cycles a patient will receive based on whether they will be eligible for cabazitaxel or not. This has been adjusted in the results by the Commentary so that a consistent number of cycles is given to all patients who are eligible. This was changed by the Commentary as the number of cycles would be determined by eligibility by the PET/CT and response to treatment.

- When determining the net cost the ADAR applies the 15% patient reimbursement to the PET scan and the PSMA targeted therapy. However, the GPG of $98.70 applies as these are outpatient procedures that are greater than $658.35 (as of November 2023). This has been adjusted for by the Commentary.

Results from the ADAR are presented in Table 12, and adjustments to the results by the Commentary are provided (shaded cells), with numbers to reflect the incremental adjustments done and the impact on the financial implications. The adjustments by the Commentary are done in the following steps.

1) Recently decreased price for cabazitaxel so the weighted average DMPQ is $272.95.
2) All patients that are eligible for ^{177}Lu PSMA receive the same number of cycles, 4.17 as it is determined by the results of the PET scan and patients' response to treatment.
3) The split between treatment with cabazitaxel and best supportive care is changed to 25% cabazitaxel and 75% best support care to reflect the discussion in the MSAC 1686 July 2002 PSD.
4) The rebate is adjusted for the greatest permissible gap (GPG) as both the ^{68}Ga PET scan and ^{177}Lu-PSMA are greater than the $658.35 (as of 1 Nov 2023). The GPG is set at $98.70 as of 1 November 2023. The cost to Medicare of the PET scan is $1,846.30 (assuming a fee of $1,945) or $1,746.30 (assuming a fee of $1,845), see above. A benefit of $80 would apply to CT (85% benefit of the $100 schedule fee, minus an additional $5 for the Multiple Services Rule in the DIST) and should be added, resulting in a total cost for PET/CT of $1,926.30 or $1,826.30. The cost of ^{177}Lu-PSMA is $7,901.30 per cycle.

The ADAR reports a net cost to the MBS of PSMA PET/CT of $1.3 million in Year 1 increasing to $2.8 million in Year 6 and a net financial impact to the MBS and PBS/RPBS (taking into account changes in costs of therapies) of $19.9 million in Year 1 and $42.7 million in Year 6. Adjustments to the inputs increases the cost to Medicare to $23.2 million in Year 1 and $49.9 million in Year 6. Uncertainty analyses presented in the ADAR showed the main area of uncertainty identified was the proportion of patients to take up the therapy.

Table 12 Financial implications of listing PSMA PET/CT and PSMA targeted therapies

Net financial impact	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Net cost to the MBS for PSMA PET/CT ($1,738.25)	$1,305,426	$1,520,730	$1,771,828	$2,064,699	$2,405,566	$2,802,238
4) GPG ($1,926.30) [Commentary]	$1,446,651	$1,685,248	$1,963,510	$2,288,066	$2,665,809	$3,105,394
4) GPG ($1,826.30) [Commentary]	$1,371,551	$1,597,761	$1,861,578	$2,169,285	$2,527,419	$2,944,183
Net cost to the MBS for Others	$19,547,094	$22,780,167	$26,544,740	$30,933,611	$36,041,054	$41,984,394
2) Cycles 4.17 [Commentary]	$18,796,820	$21,906,150	$25,526,408	$29,746,955	$34,658,490	$40,373,849
2) Cycles 4.17 + 3) Split in cabazitaxel use change to 25% [Commentary]	$19,025,965	$22,175,718	$25,842,592	$30,116,420	$35,089,458	$40,876,165
Net financial impact to MBS	$20,852,520	$24,300,897	$28,316,567	$32,998,310	$38,446,620	$44,786,632
2) Cycles 4.17 [Commentary]	$20,102,246	$23,426,879	$27,298,235	$31,811,654	$37,064,056	$43,176,087
2) Cycles 4.17 + 3) Split in cabazitaxel use change to 25% [Commentary]	$20,331,391	$23,696,448	$27,614,419	$32,181,119	$37,495,024	$43,678,403
Net financial impact to PBS/RPBS	-$982,866	-$1,125,084	-$1,304,235	-$1,517,363	-$1,766,797	-$2,057,595
1) Impact of reduction in cabazitaxel price [Commentary]	-$898,793	-$1,028,591	-$1,192,243	-$1,387,015	-$1,614,997	-$1,880,797
1) Impact of reduction in cabazitaxel price + 3) Split in cabazitaxel use change to 25% [Commentary]	-$331,023	-$363,172	-$413,188	-$477,335	-$554,206	-$644,564
Net financial impact (MBS+PBS/RPBS)	$19,869,654	$23,175,813	$27,012,333	$31,480,947	$36,679,823	$42,729,037
1) Net financial impact (reduction in cabazitaxel price) [Commentary]	$19,953,727	$23,272,306	$27,124,324	$31,611,295	$36,831,623	$42,905,835
1) Net financial impact (reduction in cabazitaxel price) + 2) Cycles 4.17 [Commentary]	$19,203,452	$22,398,289	$26,105,992	$30,424,639	$35,449,059	$41,295,290
1) Net financial impact (reduction in cabazitaxel price) + 2) Cycles 4.17 + 3) Split changes to cabazitaxel use of 25% & BSC 75% [Commentary]	$20,000,367	$23,333,275	$27,201,231	$31,703,784	$36,940,818	$43,033,839
1) Net financial impact (reduction in cabazitaxel price) + 2) Cycles 4.17 + 3) Split changes to cabazitaxel use of 25% & BSC 75% 4) + GPG ($1,926.30+$7,901.30) [Commentary]	$23,245,372	$27,113,478	$31,605,608	$36,836,177	$42,920,532	$49,999,592
1) Net financial impact (reduction in cabazitaxel price) + 2) Cycles 4.17 + 3) Split changes to cabazitaxel use of 25% & BSC 75% 4) + GPG ($1,826.30+$7,901.30) [Commentary]	$23,170,272	$27,025,992	$31,503,677	$36,717,397	$42,782,142	$49,838,382

Net financial impact	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
1) Net financial impact (reduction in cabazitaxel price) + 2) Cycles 4.17 + 3) Split changes to cabazitaxel use of 25% & BSC 75% 4) + GPG ($1,826.30+$6,410.30) [Commentary]	$18,968,207	$22,130,880	$25,800,300	$30,071,289	$35,038,810	$40,818,195
1) Net financial impact (reduction in cabazitaxel price) + 2) Cycles 4.17 + 3) Split changes to cabazitaxel use of 25% & BSC 75% 4) + GPG ($1,926.30+$6,410.30) [Commentary]	$19,043,307	$22,218,367	$25,902,232	$30,190,070	$35,177,200	$40,979,405
1) Net financial impact (reduction in cabazitaxel price) + 2) Cycles 4.17 + 3) Split changes to cabazitaxel use of 25% & BSC 75% 4) + GPG ($1,826.30+$9,544.30) [Commentary]	$27,800,716	$32,420,136	$37,788,484	$44,041,042	$51,314,868	$59,778,131
1) Net financial impact (reduction in cabazitaxel price) + 2) Cycles 4.17 + 3) Split changes to cabazitaxel use of 25% & BSC 75% 4) + GPG ($1,926.30+$9,544.30) [Commentary]	$27,875,816	$32,507,622	$37,890,415	$44,159,822	$51,453,259	$59,939,342

15. Other relevant information

Nil.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- As the proposal to create a new MBS item for a radioisotope specific (^{68}Ga)-PSMA PET/CT is aimed at assessing eligibility for PSMA targeted therapies, of which none are currently funded on the MBS (or PBS), there is no current clinical need for this test, at this time.
- The proposed fee of $1,945 is much higher than that of other current PSMA PET MBS items and the proposed fee in codependent MSAC applications 1686/1686.1 previously considered by MSAC in July 2022 and July 2023, respectively. A fee of $1,300 ($1,400 if claimed with the CT attenuation item) may be more appropriate and aligns with the current MBS items. The higher fee would require evidence demonstrating improved health outcomes in those identified and treated with PSMA-targeted radioligand therapy (i.e. ^{177}Lu PSMA therapy) using the specific investigative product for ^{68}Ga-PSMA PET/CT compared with other available radiopharmaceutical tracers used for PSMA PET/CT imaging. ESC noted this evidence was currently lacking in the ADAR.
- The only specified comparator is "no diagnostic test". As above, an additional relevant comparison is between ^{68}Ga-PSMA PET/CT with subsequent treatment with a PSMA targeted therapy versus other available radiopharmaceutical tracers used for PSMA PET/CT with subsequent PSMA targeted therapy.
- The case for removing the restriction of "once per lifetime" from the MBS item descriptor can only be assessed if there is evidence supporting retreatment, which is currently lacking.

Economic issues:

- The economic evaluation does not clearly capture the benefit of the proposed investigative test in guiding access to PSMA-targeted radioligand therapy compared with all other alternative investigative options. An additional relevant comparison may be between the ^{68}Ga and other available radiopharmaceutical tracers used for PSMA PET/CT tests, to determine which is the most cost-effective investigative test to guide access to ^{177}Lu PSMA therapy.
- A comparator split of 75% cabazitaxel and 25% best supportive care (BSC) was used, resulting in an ICER of $165,086/QALY. However, in its consideration of MSAC application 1686, MSAC had considered a comparator split of 25% cabazitaxel and 75% BSC to be more appropriate (due to the toxicity of cabazitaxel). This resulted in a reduced ICER of $123,611/QALY, however this ICER is still high and uncertain.
- The time horizon of 10 years in the base case is too long. In its consideration of MSAC application 1686.1 MSAC expressed a preference for a more conservative time horizon of 5 years, but considered a 7.5 year time horizon would be likely to be acceptable.

- The economic model assumed that BSC drug costs were zero (offset in both arms), but this assumes that the same type and dosage of drugs are used in both the intervention and comparator arms. This is uncertain and therefore BSC drug costs should be included in the model. Additionally, costs associated with the treatment of bone pain were not included.
- The ADAR for MSAC application 1686.1 (as considered by MSAC in July 2023) proposed splitting treatment into initial (2 cycles) and continuing (up to 4 cycles) treatment (maximum of 6 cycles). Only those patients who had not developed disease progression would be eligible for continuing ^{177}Lu PSMA therapy. The implications for this regimen on the economic model have not and could not be explored.

Financial issues:

- The greatest impact to the financial estimates was the assumed price of ^{177}Lu PSMA therapy (based on application 1686.1 for ^{177}Lu PSMA i&t). Given no PSMA-targeted therapies are currently funded on the MBS or PBS, the costs associated with treatment is an area of uncertainty.

Other relevant information:

- If MSAC supports funding the proposed investigative test to identify those eligible for PSMA-targeted radioligand therapy, MBS listing will be contingent on TGA approval for the additional indication of "patients who are candidates for PSMA targeted therapy", as well as MSAC support and listing of MBS items for the therapeutic intervention (not proposed in this application).

ESC discussion

ESC noted that this application from Telix Pharmaceutical Ltd requested Medicare Benefits Schedule (MBS) listing of the ILLUCCIX® Kit (kit for the preparation of gallium-68 [^{68}Ga] labelled prostate-specific membrane antigen [PSMA]-11 injection) for assessing the eligibility of patients diagnosed with metastatic castration-resistant prostate cancer (mCRPC) to undertake PSMA targeted therapy.

ESC noted that the applicant-developed assessment report (ADAR) only requested MBS funding for an investigative test, PSMA positron emission tomography/computed tomography (PSMA PET/CT), and not for the associated therapeutic intervention (PSMA targeted therapy). This is unlike MSAC applications 1686 and 1686.1, which also requested MBS funding for the therapeutic intervention (included in the codependent application).

ESC noted that the ADAR stated that an application had been submitted to the Therapeutic Goods Administration (TGA) for the additional indication of "patients who are candidates for PSMA targeted therapy" which is the subject of this current application. ESC advised that the applicant should provide an update on the TGA status of this application. ESC noted that, if MSAC supported funding this investigative test, MBS listing would be contingent on TGA approval of the additional indication, as well as MSAC support and listing of MBS items for the therapeutic intervention (not proposed in this application).

ESC considered that as the proposed test is aimed at assessing eligibility for PSMA targeted therapies, of which none are currently funded on the MBS (or PBS), there is no current clinical need for this test, at this time. On the other hand, although not funded on the MBS, MSAC deferred its consideration of application 1686.1 for Luteium-177 PSMA imaging & therapy (^{177}Lu PSMA i&t) for mCRPC at its July 2023 consideration, which this application

(1720) proposes a new investigative option (at a higher fee) for identifying those eligible for PSMA-targeted radioligand therapies in a similar population.

ESC considered several issues with the proposed MBS item descriptor. ESC noted that the proposed item descriptor specified ^{68}Ga, thereby restricting use of this item to that specific radiopharmaceutical. ESC noted that the ADAR provided no evidence to support restricting use to ^{68}Ga (other than this was the radiopharmaceutical used in the two trials used as the evidence base for the ADAR [VISION[6] and TheraP[7]]), ESC considered that there was no reason for the item descriptor to restrict use to ^{68}Ga, especially as it would be inconsistent with other staging items. In addition, ESC also noted it would also be inconsistent with the proposed investigative item for PSMA PET/CT item in application 1686/1686.1 which was radiotracer agnostic and previously considered by MSAC in July 2022 and July 2023, respectively.

ESC also considered that the item descriptor should remove reference to CT. ESC noted that other current MBS items for PSMA PET (61563 and 61564) do not include reference to CT, and that CT attenuation MBS item 61505 will generally be claimed with the items. This meant that consistent with current practice for existing PET items, amending the item to a PET item would allow the item to be eligible to be co-claimed with item 61505. Additionally, the proposed investigative PSMA-PET/CT item descriptor for MSAC applications 1686/1686.1 did not refer to CT. ESC noted that the pre-ESC response accepted that the reference to CT could be removed from the item descriptor.

ESC noted that the item descriptor refers to the test being "performed for the patient selection of PSMA-targeted radioligand therapy". However, this is not consistent with the population specified in the PICO criteria (from the ADAR) or the proposed item descriptor for MSAC applications 1686 and 1686.1, which also better aligned with the patients described in the evidence base. ESC queried whether this issue could be overcome by specifying the item number for PSMA-targeted radioligand therapy in the proposed item descriptor or rephrasing the item descriptor as suggested in the pre-ESC response.

ESC noted that the item descriptor proposes restricting the item to "once per lifetime". ESC considered that this was suitable for patients who first test negative, as there is no redifferentiation (i.e. if a patient tests negative, they remain negative). However, if a patient tests positive and is successfully treated, there may be a role for repeat scanning as there is a possibility that they may test negative later. ESC also noted that many centres rechallenge patient response. However, ESC considered that a lifetime number could only be assessed if there was evidence supporting retreatment. This evidence was currently lacking, but ESC queried whether that this could change in the future. ESC noted the frequency restriction for the proposed investigative item in this application was different to the proposed investigative item in application 1686/1686.1 considered by MSAC in July 2022 and July 2023, respectively.

ESC noted that the proposed item descriptor includes a fee of $1,945. This is greater than the fee of $1,300 ($1,400 if claimed with MBS item 61505) for both the current PSMA PET MBS items (61563 and 61564) and of that proposed in MSAC applications 1686/1686.1.

[6] Sartor, O., et al., *Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer.* The New England journal of medicine, 2021. **385**(12): p. 1091-1103.
[7] Hofman, M.S., et al., *[(177)Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial.* Lancet, 2021. **397**(10276): p. 797-804

ESC noted that the fee includes the cost of a single cold kit (three doses), which is $[redacted] (or $[redacted] per dose).

ESC considered that a fee of $1,300 (or $1,400) was more appropriate for the proposed service and aligned with current PSMA PET (tracer agnostic) MBS items. Alternatively, ESC queried whether the fee should be based on the cost per patient ($1,412). ESC considered that the higher fee proposed by the applicant may reflect the increased expense of obtaining supply of the specific radiopharmaceutical from a specific manufacturer. ESC considered that, although expensive, this cold kit could provide advantages in more rural areas. However, ESC advised that the higher fee would require evidence demonstrating improved health outcomes in those identified and treated with PSMA-targeted radioligand therapy using the specific investigative product for ^{68}Ga-PSMA PET/CT compared with other available radiopharmaceutical tracers used for PSMA PET/CT imaging. ESC noted this evidence was currently lacking in the ADAR.

After considering all these issues with the proposed item descriptor, ESC suggested the following revisions (in red).

Category 5 – DIAGNOSTIC IMAGING SERVICES

MBS XXXX

Whole body ^{68}~~Ga~~ prostate-specific membrane antigen (~~68Ga~~-PSMA) positron emission tomography (PET)~~/computerised tomography (CT)~~ study performed for patient selection for patients who would be eligible for PSMA targeted radioligand therapy under item XXXX.

Applicable only once per lifetime

Fee: $1,300.00 Benefit: 75% = $975.00 85% = $1,201.30

ESC noted and welcomed consultation input from 1 professional organisation (the Australasian Association of Nuclear Medicine Specialists) and 1 individual who was a medical specialist, both of which were supportive of the application.

ESC noted that in the VISION and TheraP trials, 85% and 90% of patients, respectively, met the nominated eligibility criteria for PSMA PET/CT, which is a high proportion and makes the requirement for prior testing potentially unclear especially when considered with recent retrospective data from the Re-SPECT study reported by Emmett (2023)[8] which found that despite these uptake values, among men treated with ^{177}Lu PSMA i&t, 31% were considered limited or non-responders. However, ESC noted in this respect that it was clinically inappropriate to treat patients with a futile therapy, especially if it is costly and therefore it was important for there to be a test which was sufficiently discriminatory between responders and non-responders.

ESC noted that the ADAR specified the comparator to be no diagnostic test. ESC noted that the ADAR compared treatment with a PSMA targeted therapy with treatment with best supportive care (BSC) or cabazitaxel based on determination of eligibility using imaging with Ga-68 PSMA while the Commentary proposed that the ideal comparison should be between treatment with a PSMA targeted therapy and no diagnostic test and treatment with a PSMA

[8] Emmett L, John N, Pathmanandavel S, Counter W, Ayers M, Sharma S et al. (2023). Patient outcomes following a response biomarker-guided approach to treatment using 177Lu-PSMA-I&T in men with metastatic castrate-resistant prostate cancer (Re-SPECT). Ther Adv Med Oncol 15:1–11.

targeted therapy based on determination of eligibility using imaging with Ga68 PSMA (for which there was no evidence).

However, ESC considered that an additional relevant comparison is between ^{68}Ga-PSMA PET/CT with subsequent treatment with a PSMA targeted therapy versus other available radiopharmaceutical tracers used for PSMA PET/CT with subsequent PSMA targeted therapy (i.e. ^{177}Lu PSMA therapy), to capture the relative benefit of the ^{68}Ga vs the -PSMA PET/CT test.

ESC noted that the ADAR provided no new clinical trial data on comparative safety or effectiveness for the diagnostic test. Clinical trial data for PSMA targeted therapy were from the VISION and TheraP trials, which were the evidence base for applications 1686/1686.1 so have already been considered by MSAC.

ESC noted that, in the trials, patients were selected based on results from both ^{68}Ga PET/CT and fluorodeoxyglucose (FDG) PET/CT. However, ESC noted that FDG PET/CT is not part of the standard diagnostic imaging for prostate cancer, and there are different models on how much testing should be undertaken to select patients – for example, the Peter MacCallum Cancer Centre use both types of imaging, but the VISION trial only used PSMA PET/CT.

ESC noted that the economic evaluation used a base case weighted comparator of 75% cabazitaxel and 25% best supportive care (BSC). This resulted in an incremental cost-effectiveness ratio (ICER) of $165,086 per quality-adjusted life year (QALY). However, in its consideration of application 1686, MSAC had agreed that a weighting of 25% cabazitaxel and 75% BSC was more appropriate. This resulted in an ICER of $123,611/QALY.

ESC noted an applicability issue with the model insofar as for the comparison against cabazitaxel, efficacy data for both ^{177}Lu PSMA i&t and cabazitaxel were sourced from the TheraP trial which compared ^{177}Lu PSMA i&t against cabazitaxel, whereas for the comparison against BSC, efficacy data for both ^{177}Lu PSMA i&t and BSC were sourced from the VISION trial which compared ^{177}Lu PSMA and BSC against BSC alone. ESC also noted that the economic model assumed that drug costs were zero because they were offset in both arms. However, ESC considered this may not be appropriate, as it assumes the same type and dosage of BSC drugs are used in both the intervention and comparator arms. In addition, ESC noted that this assumption meant that it was assumed there were no BSC drug costs in the proportion of patients in the 177Lu-PSMA vs BSC comparison whereas the clinical evidence informing the survival curves incorporated BSC drug use in both arms.

ESC noted that the economic evaluation used a hybrid model of a decision tree and a partitioned survival model (PSM) with a proportional hazards approach. ESC noted that the models used Kaplan–Meier (KM) curves for each individual arm of the trials that were independently extrapolated using parametric curves, with extrapolation applied from when 10% of patients remained “at risk” and continuing to a 10-year time horizon. ESC noted that the 10-year time horizon, while consistent with the base case assumption for application 1686, had not been considered reasonable by MSAC. Subsequently, MSAC expressed a preference for a more conservative time horizon of 5 years, but considered a 7.5 year time horizon would be likely to be acceptable (MSAC application 1686.1 public summary document).

ESC also noted that the model assumed that only patients remaining progression-free would continue with therapy, up to a maximum of 6 cycles. The ADAR for MSAC

application 1686.1 (as considered by MSAC in July 2023) proposed splitting treatment into initial treatment (2 cycles) and continuing treatment (up to 4 cycles). The purpose of doing this was to ensure that re-evaluation occurred for eligibility, as retrospective data from the Re-SPECT suggested that a high percentage of patients progressed on or before the second cycle. For continuing treatment, only those who had not developed disease progression while receiving ^{177}Lu PSMA i&t for this condition would be eligible. ESC noted from the commentary that the implications for this regimen have not and could not be explored. However, the additional 4 cycles depended on not having disease progression, which was the same as the model – the only difference was the initial 2 cycles. The number of PSMA cycles in the model was 4.17.

As discussed previously ESC considered that the economic evaluation was not capturing the correct comparison. ESC considered that an additional relevant comparison may be ^{68}Ga PSMA PET/CT with subsequent treatment with a PSMA targeted therapy vs PSMA PET/CT using other available radiopharmaceutical tracers with subsequent PSMA targeted therapy, as this would capture the relative benefit of ^{68}Ga PSMA PET/CT vs other available radiopharmaceutical tracers to be used with PSMA PET/CT.

ESC noted that there were assumptions in the model regarding adverse event (AE) costs, and AE disutilities which favoured the intervention but these had a minor impact on the ICER. ESC noted that costs associated with the treatment of bone pain (e.g. opioids, ^{89}strontium, local radiotherapy) were also not included, which assumes the same efficacy for ^{177}Lu PSMA, BSC and cabazitaxel in addressing bone pain. ESC noted that the total cost of ^{177}Lu PSMA treatment ($8,000) was assumed to be consistent with MSAC application 1686, although there were modifications to how the cost was generated.

ESC noted that the main drivers of the economic model were the cost of ^{177}Lu PSMA therapy, extrapolation of progression-free survival (PFS) and overall survival (OS) for both cabazitaxel and ^{177}Lu PSMA, the proportion of patients receiving cabazitaxel, and the time horizon (decreasing the time horizon to 5 years increased the ICER by approximately 46%). Also, the use of different utility measurement tools affected utility values as using two alternative instruments (the EORTC-8D and EQ-5D-5L instruments) reduced the ICER by 13% and 11% respectively. ESC also noted from the Commentary that Lloyd et al. (2015)[9] described four types of participants with mCRPC, and that the populations used in the ADAR (populations 1 and 2) may be misleading; populations 3 and 4 (after failure of androgen deprivation therapy, currently receiving chemotherapy or post-chemotherapy) appeared to be the most reflective of the proposed population for utilities for PFS.

ESC noted that an epidemiological approach was used to estimate the financial impacts. This relied on the eligible population numbers and many of the assumptions reported in MSAC application 1686. However, the ADAR made the following changes to the assumptions:

- Uptake in the first year for therapy is 25% (or 676 total eligible patients), increasing by 15% each year to 50.3% (1,451 patients) by Year 6. Evidence to support this assumption was not presented but the uptake was deemed reasonable by the Commentary because it assumes that at least half of the eligible patients will have access to this treatment by Year 6.

[9] Lloyd et al. Health-Related Quality of Life and Health Utilities in Metastatic Castrate-Resistant Prostate Cancer: A Survey Capturing Experiences from a Diverse Sample of UK Patients. Value Health. 2015 Dec;18(8):1152-7. doi: 10.1016/j.jval.2015.08.012. Epub 2015 Oct 21. PMID: 26686802.

- The ADAR adjusts the population for whether they receive cabazitaxel or docetaxel as subsequent treatment. This is only applied to patients who are assumed to have progressed, which means that different proportions are receiving subsequent treatment across the arms. Although it is implied that patients who have progressed would receive subsequent therapy, the evidence used for this proportion only reports that 14.9% of the intention-to-treat population received subsequent treatment.
- The ADAR reports results based on a split of 75% cabazitaxel and 25% BSC in the comparator arm. However, based on the toxicity of cabazitaxel, this was adjusted in the Commentary to 25% cabazitaxel and 75% BSC.
- The ADAR applies different assumptions about the number of PSMA targeted therapy cycles a patient will receive based on whether they will be eligible for cabazitaxel or not. The Commentary adjusted this to an average of 4.17 cycles.
- For the net cost, the ADAR applies the 15% patient reimbursement to the PET scan and the PSMA targeted therapy. However, the greatest permissible gap of $98.70 applies, as these are outpatient procedures that are greater than $658.35 (as of November 2023). This has been adjusted for by the Commentary.

ESC noted that the net cost to the MBS of PSMA PET/CT alone is $1.3 million in Year 1 increasing to $2.8 million in Year 6 while the net financial impact for the whole combined test and therapy was estimated to be $19.9 million in Year 1 increasing to $42.7 million in Year 6 while adjustments to the inputs by the commentary increased the impact to $23.2 million in Year 1 to $49.9 million in Year 6. Based on analyses presented in the ADAR, the main area of uncertainty was the proportion of patients taking up the therapy. In the pre-ESC response, the applicant provided updated financial estimates with updated costs as suggested in the Commentary taking into account the recent November 2023 Medicare Benefits Schedule (MBS) updates and Greatest Permissible Gap (GPG). This resulted in a net financial impact to the MBS of $33.6 million in Year 1 increasing to $72.5 million in Year 6.

17. Applicant comments on MSAC's Public Summary Document

Telix Pharmaceuticals thanks the MSAC and its subcommittees for consideration of this application and looks forward to progressing this application further such that Medicare funding for 68Ga PSMA-11 PET/CT imaging for patients who are candidates for PSMA targeted therapy is publicly reimbursed to allow prostate cancer patients access.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website