Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1686.1 – [177]Lutetium PSMA i&t for metastatic castrate resistant prostate cancer

Applicant: A group of academic specialists, co-sponsored by the Australasian Association of Nuclear Medicine Specialists (AANMS)

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

This fit-for-purpose Department contracted assessment report (FFP DCAR) presents an updated economic evaluation and financial analyses to the Medical Services Advisory Committee (MSAC) for Medicare Benefits Schedule (MBS) funding for two technologies – one therapeutic (1) and one investigative (2).

The proposed therapeutic intervention for MBS listing is:

1. [177]Lutetium (Lu) PSMA: According to the proposed item descriptors, this should also specify 24-hour post-therapy single-photon emission/computed tomography/computerised tomography (SPECT/CT)

for which treatment eligibility is determined by:

2. Diagnostic test: whole body prostate specific membrane antigen [PSMA] positron emission tomography [PET]/computerised tomography [CT];

for the treatment of progressive or symptomatic metastatic castrate resistant prostate cancer (mCRPC) in patients who have received at least one androgen receptor signalling inhibitor as well as at least one line of chemotherapy (docetaxel +/- cabazitaxel), both of which are subsidised via the PBS and RPBS.

The request is consistent with the ratified PICO Confirmation. However, as for the original and resubmission ADARs, the request no longer requires "Diagnostic test 2: Whole body ^{18}F-fluorodeoxyglucose (FDG) PET/CT – FDG PET/CT" following whole body PSMA PET/CT to be eligible for ^{177}Lu PSMA i&t. The applicant advised this was the intention of its comments on the ratified PICO Confirmation.

Consistent with the previous public summary documents for application 1686/1686.1, MSAC has referred to specific [177]LuPSMA products, either as ^{177}Lu PSMA imaging scan and therapy (^{177}Lu PSMA i&t) or ^{177}Lu PSMA-617.

2. MSAC's advice to the Minister

MSAC considered the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost of 177 lutetium prostate-specific membrane

antigen imaging scan and therapy (^{177}LuPSMA i&t). On the basis of the current evidence and on the premise that providers will have a legal right to use ^{177}LuPSMA i&t in Australia if the application is approved, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for: 1) ^{177}Lu PSMA 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 ^{177}Lu PSMA i&t.

MSAC considered afresh the evidence comparing ^{177}Lu PSMA i&t and ^{177}Lu PSMA-617 products, and additional input provided about this issue. MSAC determined 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 high certainty from the evidence that ^{177}Lu PSMA i&t therapy is acceptably safe and effective.

MSAC considered that its previous uncertainties regarding the economic and financial analyses had been sufficiently addressed. Despite limitations in the revised economic evaluation, MSAC was satisfied the incremental cost-effectiveness ratio (ICER) range provided reliable estimates for the upper limit of cost-effectiveness of ^{177}Lu PSMA i&t over its comparators of best supportive care, and cabazitaxel. Although the ICER was high, MSAC accepted that ^{177}Lu PSMA i&t was cost effective in the context of a population with high clinical need, consumer preference for ^{177}Lu PSMA therapy over its comparators and an equity of access issue as some patients are currently paying for the treatment privately or are receiving treatment funded through the Department of Veterans' Affairs. MSAC also considered that the financial impact was acceptable for this well-defined population.

MSAC noted the previous and current information concerning a patent related dispute between the applicants and a commercial organisation. MSAC considered that determining the patent issue is outside the MSAC Terms of Reference, but noted that the patent related matters would require consideration by government and the Minister prior to any decision in relation to whether to list new MBS items as a result of this application.

MSAC supported MBS item descriptors agnostic to the type of ^{177}Lu PSMA therapy:

Category 5 - Diagnostic Imaging Services
MBS item XXXX 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. (R) (Anaes)
Fee: $1,300 Benefit: 85% = $1,201.30*

Category 3 - Therapeutic Procedures T3. Therapeutic Nuclear Medicine
MBS item ZZZZ Treatment phase: initial treatment Administration of Lutetium 177 PSMA followed 24 hours later by whole body Lu-PSMA single-photon emission computed tomography (SPECT) for treatment of a patient with metastatic castrate resistant prostate cancer, who is PSMA-positive as determined by PSMA PET defined as SUVmax >15 at a single site of disease and SUVmax >10 at all sites of measurable disease, after progressive disease has developed while on at least one taxane chemotherapy and at least one androgen receptor signalling inhibitor A patient is eligible to claim once per cycle up to a maximum of 2 cycles in the initial treatment phase.
Fee: $8,000 Benefit: 85% = $7,901.30*

Category 3 - Therapeutic Procedures T3. Therapeutic Nuclear Medicine
MBS item YYYY Treatment phase: continuing treatment Administration of Lutetium 177 PSMA followed 24 hours later by whole body Lu-PSMA single-photon emission computed tomography (SPECT) for treatment of a patient with metastatic castrate resistant prostate cancer, if: • a service to which item ZZZZ has been provided; and • the patient must not have developed disease progression while receiving Lutetium 177 PSMA for this condition Disease progression for the purposes of administering MBS item YYYY is defined as a rise in PSA of > 2 ng/mL confirmed by 2 tests a minimum 2 weeks apart and/or evidence of new soft tissue metastases on diagnostic CT as per RECIST criteria. A patient is eligible to claim once per cycle up to a maximum of 4 cycles in the continuing treatment phase.
Fee: $8,000 Benefit: 85% = $7,901.30*

*85% benefit reflects the 1 November 2023 Greatest Permissible Gap (GPG) of $98.70. All out-of-hospital Medicare services that have an MBS fee of $658.35 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

Consumer summary
This is a reapplication from a group of academic specialists, co-sponsored by the Australasian Association of Nuclear Medicine Specialists, requesting Medicare Benefits Schedule (MBS) listing of [177]Lutetium prostate-specific membrane antigen (^{177}Lu-PSMA) therapy to treat patients with metastatic castrate-resistant prostate cancer. Also requested is MBS listing of whole-body PSMA positron emission tomography (PET)/computerised tomography (CT), which will be used to determine treatment eligibility. MSAC previously considered this application in July 2022 and July 2023.

Consumer summary

Metastatic castrate-resistant prostate cancer is a type of advanced prostate cancer that has spread to other parts of the body and is not responding 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 PET/CT scan. The scan is of the whole body. If patient's prostate cancer cells are found to have high levels of PSMA, they may be eligible for a new therapy that targets the cells that contain PSMA. The new therapy is called PSMA-targeted radionuclide therapy. It is for patients with metastatic castrate-resistant prostate cancer. This new therapy uses a radioactive chemical (also known as a radionuclide) called Lutetium. The Lutetium is connected to a molecule that fits into the PSMA receptor on prostate cancer cells. When the molecule attaches to the PSMA receptor, the radioactive chemical can enter the prostate cancer cell and kill it. [177]Lu PSMA i&t is a type of PSMA targeted radionuclide therapy.

The resubmission proposes a two-step approach to ^{177}Lu PSMA i&t therapy (referred to as Lutetium 177 PSMA in the proposed MBS items). In this approach, all patients who are eligible will receive an initial two cycles (doses) of ^{177}Lu PSMA i&t therapy. All patients will then have blood tests and scans to see how well they have responded to the treatment. If they have responded well, they will be eligible to continue treatment for another four cycles. If the tests show no improvement despite ^{177}Lu-PSMA i&t treatment, it will be recommended that the patient stops ^{177}Lu PSMA i&t and tries a different treatment instead.

MSAC acknowledged the high clinical need for this therapy, and that both patients and consumers prefer it over other last-line options because of its tolerability (in that it only produces mild side effects). MSAC also noted the current issues with equity of access, as the treatment is only performed at specialty centres and has high out-of-pocket costs.

MSAC considered that its previous uncertainties about the economic and financial aspects of the proposed scan and treatments had been resolved. MSAC considered that the treatment represented good value for money for a patient population with high clinical need. In addition, MSAC considered that the proposed price for ^{177}Lu PSMA i&t compared favourably to how much the treatment costs to perform overseas. Additionally, MSAC considered it unlikely that the eligible patient population would grow in size significantly, so the overall budget impact would remain moderate.

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

MSAC supported MBS funding of 1) ^{177}Lu PSMA i&t therapy for the treatment of patients with metastatic castrate-resistant prostate cancer, and 2) whole-body PSMA PET/CT to identify those eligible for ^{177}Lu PSMA i&t therapy. MSAC considered ^{177}Lu PSMA i&t therapy to be safe, effective and good value for money for a well defined group of eligible patients with advanced disease. MSAC recommended that utilisation and budget impact be reviewed after two years, to ensure the service is being used appropriately.

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

MSAC noted that this reapplication from a group of academic specialists, co-sponsored by the Australasian Association of Nuclear Medicine Specialists, was requesting Medicare Benefits Schedule (MBS) listing of [177]Lutetium prostate-specific membrane antigen (^{177}Lu-PSMA) therapy for the treatment of progressive or symptomatic metastatic castrate-resistant prostate cancer (mCRPC). Eligibility for this treatment is determined by whole-body PSMA positron emission tomography (PET) and computerised tomography (CT).

MSAC noted that the proposed therapeutic intervention includes ^{177}Lu-PSMA single-photon emission CT (SPECT) at 24 hours after each treatment. Tumour sites are measured after each treatment by taking whole-body images at 24 hours using radiation from the treatment. Patients must have received at least one androgen receptor signalling inhibitor and at least one line of chemotherapy (docetaxel +/– cabazitaxel through the Pharmaceutical Benefits Scheme [PBS]/Repatriation PBS [RPBS]).

MSAC recalled that it had previously considered this application at its July 2022 and July 2023 meetings. At its most recent consideration, MSAC had accepted the previous evidence that ^{177}Lu PSMA i&t therapy was acceptably safe and effective but continued to have concerns that the incremental cost-effectiveness ratio (ICER) was too high and uncertain. In July 2023, MSAC had noted that the resubmission included a substantially changed item descriptor to reflect a newly proposed two-step treatment algorithm, separated into two MBS items: one for initial treatment (up to a maximum of two cycles) and one for continuing treatment (up to a maximum of four additional cycles). However, this two-step approach was not captured by the structure of the economic model. MSAC had also noted other modelling issues, including the use of patient-level data from two different trials. MSAC therefore deferred its advice at the time and requested that a revised economic evaluation be conducted, with the model structure corrected to capture the two-step approach to treatment. MSAC had also requested a revision to the model to reduce the uncertainty created by the patient-level data from different trials in the same model for determination of progression-free survival (PFS) benefits and costs associated with the intervention. MSAC also requested better justification (or removal) of the selected treatment-specific utility weights. Finally, although MSAC had preferred a more conservative time horizon of 5 years, it had considered a 7.5-year time horizon would likely be acceptable (1686.1 public summary document [PSD]).

MSAC noted that a fit-for-purpose (FFP) Department-contracted assessment report (DCAR) was commissioned to progress the MSAC deferral and the Committee's requested revisions to the economic model.

MSAC acknowledged the high clinical need for this comparatively safe and effective intervention. MSAC noted that the treatment has been successfully delivered in several specialty centres in Australia for the past 10 years and is currently funded through the Department of Veterans' Affairs on a case-by-case basis. MSAC also noted the pre-MSAC response emphasised the strong consumer and clinician preference for this treatment over alternatives because of its superior safety, effectiveness and tolerability (in that it has relatively mild side effects). However, MSAC noted equity issues, as some patients may be paying for the treatment privately at a cost of $12,000–$30,000. There were also barriers to access in remote and regional areas.

MSAC noted the support for this application from all consumer and patient advocacy organisations, and that most other organisations who provided consultation input were supportive of the application. MSAC also noted and considered the consultation input from those who were not supportive of the application, including from a commercial organisation who reiterated a previous submission that there was insufficient evidence to support the therapeutic equivalence between ^{177}Lu PSMA i&t and ^{177}Lu PSMA-617, and that the limited body of available data does not allow for a reliable clinical comparison between the two structurally different products (summarised at [9]).

MSAC further noted that patent-related issues arising from any manufacture, use or administration of ^{177}Lu PSMA i&t in Australia were again raised in the public consultation. In particular, MSAC noted evidence and correspondence provided to it revealing an unresolved disagreement between a commercial organisation and the applicants over patent issues associated with the proposed use of [177]LuPSMA i&t in Australia. MSAC noted that there does not

appear to have been any form of legal settlement in relation to the patent issues to date. MSAC also noted that there was no indication that there have been any Court rulings about the patent issues or that the patent disagreement is currently the subject of any legal proceeding.

MSAC noted the pre-MSAC response also provided further advice upon these matters. MSAC noted that determining and advising on patent related matters is not within its Terms of Reference and concluded that these matters would require consideration by government and in particular the Minister prior to and in the course of any decision in relation to whether to list new MBS items as a result of this application. Accordingly, MSAC conducted its analysis in relation to the comparative safety, clinical effectiveness, cost-effectiveness and total cost of [177]LuPSMA i&t on the basis of the information and evidence before it, and on the premise that providers will have a legal right to use it in Australia if the application is approved.

MSAC reconsidered the available evidence base and new information and submissions comparing ^{177}Lu PSMA i&t and ^{177}Lu PSMA-617 products. MSAC noted the Phase III trials evaluating the comparative efficacy and safety of ^{177}Lu PSMA i&t (SPLASH) and ^{177}Lu-PSMA 617 (PSMAfore) had not been previously considered as the original applicant developed assessment report (ADAR) for application 1686 excluded these trials from the literature review as they used different comparators (enzalutamide or abiraterone) to those proposed in the application. MSAC also noted the pre-MSAC response which:

- highlighted that these trials were not included in the assessment as they were not comparable studies, with different dosing regimens, therefore results reporting differences in efficacy are flawed. MSAC noted these trial populations were conducted in an earlier treatment line (ie. mCRPC post progression on androgen receptor pathway inhibitor pathway and pre-taxane chemotherapy) than proposed in the current application (i.e. mCRPC post progression after ASI [(i.e. abiraterone, enzalutamide or darolutamide via PBS/RPBS)] and taxane chemotherapy).
- stated that there were no meaningful clinical differences between Lu PSMA-617 and Lu PSMA i&t identified in daily clinical practice or in publications looking at overall survival and response rate using the two agents in Australia.

MSAC noted that the results from SPLASH and PSMAfore suggested differences in the current PFS hazard ratios (HRs) for the two products. However, MSAC considered that, due to the nature of the naïve comparison across the trials involving different cohorts of patients, the results of the comparison were unreliable. In contrast, MSAC noted the matched analysis[1] comparing ^{177}Lu PSMA-617 (n=55) and ^{177}Lu PSMA i&t (n=55) which showed that no differences were found in overall survival (OS) between treatments and the rate of clinically relevant toxicities was low for both products.

MSAC considered that there was no new substantive clinical trial data that changed MSAC's previous conclusion of mutual noninferiority for patient outcomes between the two products – [177]Lu PSMA i&t and ^{177}Lu PSMA-617 have similar safety, efficacy, biodistribution and are radioequivalent, despite both products using different dosing schedules. MSAC also acknowledged that direct evidence comparing ^{177}Lu PSMA i&t and ^{177}Lu PSMA-617 was not available and would be unlikely to eventuate. Therefore, based on the totality of the available evidence and additional perspectives comparing ^{177}Lu PSMAi&t and ^{177}Lu PSMA-617 products, MSAC reaffirmed previous conclusions that the two products are mutually noninferior for patient outcomes, and thus considered the evidence for ^{177}Lu PSMA-617 to be relevant for ^{177}Lu PSMA i&t, and therefore accepted the results of the clinical evaluation and the clinical

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[1] Hartrampf PE, Weinzierl FX, Buck AK, et al. Matched-pair analysis of [^{177}Lu]Lu PSMA I&T and [^{177}Lu]Lu PSMA-617 in patients with metastatic castration-resistant prostate cancer [published online ahead of print, 2022 Mar 4]. *Eur J Nucl Med Mol Imaging*. 2022;10.1007/s00259-022-05744-6

aspects of the modelled economic evaluation across these two ^{177}Lu PSMA products. Thus, MSAC accepted the evidence that ^{177}Lu PSMA i&t therapy is acceptably safe and effective.

MSAC noted that ^{177}Lu-PSMA i&t is currently available through the Therapeutic Good Administration (TGA) exemption for production of radiopharmaceuticals in public or private hospitals for local use and not for on-sale. The ^{177}Lu PSMA-617 product (product name pluvicto) is currently under evaluation by the TGA[2].

Regarding the item descriptors, MSAC considered it appropriate that the items are radiotracer agnostic, as proposed in this application. For the PSMA-PET item, this would be consistent with other similar items for PSMA PET on the MBS. For the therapeutic items, MSAC considered that an item agnostic to the type of ^{177}Lu PSMA therapy would ensure patient access noting the likely emergence of other ^{177}Lu PSMA products which may either become TGA approved or exempt from inclusion on the Australian Register of Therapeutic Goods (ARTG) (like ^{177}Lu-PSMA i&t product).

MSAC considered that while the conclusion of mutual noninferiority between ^{177}Lu PSMA i&t and ^{177}Lu PSMA-617 remained sound, the possibility of a claim of ^{177}Lu PSMA-617 superiority over ^{177}Lu-PSMA i&t is not precluded in the future if there was new comparative evidence to support this claim.

MSAC considered that the cost-effectiveness analysis (CEA) presented in the FFP DCAR partly addressed MSAC's previous concerns. However, the model, which was based on a hybrid approach, generated new uncertainty. MSAC noted that the model demonstrated the limitations of the data and evidence, and that applying new methods using the existing data required assumptions and/or involved input transformations that are inherently uncertain.

MSAC noted that to address the ESC's concerns regarding the uncertainty in the ICER ranges from alternative base case models (results in Table 12), an Addendum to the FFP DCAR model was prepared. This included further scenario analyses (with relevant model updates using the original partitioned survival model (PSM)) using differing clinical rules for progression to model minimum and maximum treatment discontinuations as requested by ESC. MSAC noted that the best case ICER ($113,033 per quality-adjusted life year [QALY]), which was based on all patients receiving one cycle and only those with PFS receiving subsequent treatment (absolute maximum discontinuations), was similar to the updated base case ICER ($113,346/QALY; see Table 13), based on all patients receiving the first two cycles according to the proposed item descriptor. While the worst case ICER (based on all surviving patients receiving six cycles) was $132,083/QALY, MSAC considered the most likely maximum ICER (based on all surviving patients receiving up to four cycles, from the VISION trial) was $121,535/QALY.

MSAC noted from sensitivity analyses on the updated base case that changing the effectiveness of the incremental OS benefit (relative to the comparator of best supportive care) had the largest impact on the ICER (see Table 14). Using the:

- lower-bound 95% confidence interval (CI) for OS HR (from 0.62 to 0.52) in ^{177}Lu PSMA i&t vs. best supportive care reduced the ICER to $90,807/QALY.
- upper-bound 95% CI for OS HR (from 0.62 to 0.74) in ^{177}Lu PSMA i&t vs best supportive care increased the ICER to $156,727/QALY.

MSAC also noted that changing the assumed health state utility values had moderate impact to the updated base case model ICER ranging from $98,832 to $108,711/QALY over the values

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[2] https://www.tga.gov.au/resources/prescription-medicines-under-evaluation/pluvicto-novartis-pharmaceuticals-australia-pty-ltd

tested. In multivariate analyses (using an OS HR of 0.52 in ^{177}Lu PSMA i&t vs. best supportive care, PFS of 0.86 and progressed disease [PD] of 0.635, based on Magnus et al. 2019), MSAC noted the ICER reduced to $80,129, however MSAC considered this to be uncertain. MSAC considered that, on balance, the ICER would be unlikely to be lower than $100,000/QALY as demonstrated in the additional modelling in the Addendum.

Overall, MSAC considered that its previous uncertainties regarding the economic analyses had been resolved sufficient for decision making. Despite limitations in the revised economic evaluation (as outlined above), MSAC was satisfied the ICER range provided in the Addendum provided reliable estimates for the upper limit of cost-effectiveness of ^{177}Lu PSMA i&t over its comparators of best supportive care and cabazitaxel. Although the ICER was high, MSAC accepted that ^{177}Lu PSMA i&t was cost effective in the context of a population with high clinical need, consumer preference for ^{177}Lu PSMA therapy over its comparators and an equity of access issue as some patients are currently paying for the treatment privately or are receiving the treatment funded through the Department of Veterans' Affairs. In addition, MSAC considered that the total cost per patient for ^{177}Lu-PSMA i&t in Australia ($30,440) under the proposed treatment regimen compared favourably to the cost of the treatment overseas. The driver of the incremental cost is the cost of the proposed radiopharmaceutical, which MSAC considered is unlikely to reduce in the future.

Regarding the financial impact, MSAC considered that the current estimates appeared more plausible than in previous submissions, although there was some uncertainty around the growth in uptake and MSAC noted it may be slower than what was modelled. The estimated financial impacts, based on the two-step treatment approach, were as follows:

- If all eligible patients receive the initial two cycles: $11,990,598 in Year 1 to $32,012,589 in Year 6.
- If 69% of eligible patients who respond after two cycles receive a third cycle: $15,874,383 in Year 1 to $42,381,545 in Year 6.
- If 34% of eligible patients who respond after two cycles receive a fourth cycle: $17,788,131 in Year 1 to $47,490,885 in Year 6.

Overall, MSAC considered that its previous uncertainties regarding the financial analyses had been resolved sufficient for decision making. In addition, MSAC considered the estimated eligible patient population was relatively small and well defined, so the risk of utilisation beyond the intended population was low.

MSAC recommended that utilisation (including how many cycles patients undergo) and budget impact be reviewed after two years of commencement of public subsidy.

4. Background

In its consideration of the original ADAR (MSAC 1686) in July 2022, 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 1686 PSD July 2022, p.1). 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) was too high and uncertain (MSAC 1686 PSD July 2022, p.2). Following an update of the modelled results to incorporate a price reduction for cabazitaxel, the base case ICER was estimated at $81,653/quality-adjusted life year (QALY) over a 10-year time horizon. There have been two further price reductions for cabazitaxel since July 2022. An essential structural assumption of the original model, stated as one of the key components of the economic evaluation (MSAC 1686 PSD July 2022, Table 9, p25), is that only those who remained

progression-free continued to receive ^{177}Lu PSMA i&t treatment at each cycle. After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support Application No 1686 (MSAC 1686 PSD July 2022, pp.1-2).

The resubmission ADAR (MSAC 1686.1) was considered by MSAC in July 2023. Some of the sources of uncertainty, identified by ESC at the time of consideration of the original ADAR, including the overall survival (OS) hazard ratio assumed for cabazitaxel and the time horizon, were at least partially addressed in the modelled economic evaluation in the MSAC 1686.1 ADAR

The MSAC 1686.1 resubmission ADAR substantially changed the item descriptor to reflect a new proposed two-step treatment algorithm. While the PSMA PET/CT test to determine eligibility for ^{177}Lu PSMA i&t treatment remained (Table 2), treatment with ^{177}Lu PSMA i&t was separated into two MBS items – initial and continuing, see Table 3 and Table 4, respectively.

The two-step approach to eligibility for initial (up to a maximum of 2 cycles) and continuing (up to a maximum of 4 cycles) treatment with single-photon emission SPECT/CT performed 24 hours post-infusion for each cycle, was based on the results from the Re-SPECT study (a retrospective analysis of a clinical ^{177}Lu PSMA i&t treatment program, n=116, Emmett, 2023[3]). The results from the Re-SPECT study informed the applicant's approach to provide continuing ^{177}Lu PSMA i&t treatment only to patients who did not demonstrate disease progression and ceasing ^{177}Lu PSMA i&t treatment in patients with early disease progression. MSAC noted ceasing ^{177}Lu PSMA i&t treatment in patients with disease progression after the second ^{177}Lu PSMA i&t treatment may give them the opportunity to access alternative, potentially more effective treatment (MSAC 1686.1 PSD[4] July 2023, p.4). The Re-SPECT study found that both serum prostate specific antigen (PSA) response and changes in tumour volume on a SPECT/CT scan could predict how patients responded to treatment after the second dose.

ESC considered that the change of the intervention to a two-step approach to treatment based on the Re-SPECT study presumed comparative safety and effectiveness to that previously demonstrated based on the VISION and TheraP trials. There is no clinical evidence to support this presumption.

MSAC noted that this new two-step approach had implications for the economic model (MSAC 1686.1 PSD July 2023, p.4). The MSAC 1686.1 resubmission ADAR made a few modifications to the original model in the MSAC 1686 ADAR, however, none of the changes reflected the proposed two-step treatment algorithm. MSAC noted that the proposed two-step approach to treatment was not captured by the structure of the model (MSAC 1686.1 PSD July 2023, p.1). Nevertheless, as explained below, the Commentary to the MSAC 1686.1 resubmission ADAR made the necessary amendments that reflected the two-step approach.

It was envisaged that since PSA and SPECT/CT assessment after the second ^{177}Lu PSMA i&t dose is capable of identifying "responders" and "non-responders" among the mCRPC population, the size of the population eligible for the continuing treatment (up to a total of 6 cycles) would be effectively reduced to "responders", while the treatment of "non-responders" would be limited to the first 2 cycles, suggesting an associated reduction in the cost of treatment. However, this potential for cost reduction had already been fully (albeit implicitly) realised in the original model.

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[3] 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.

[4] chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1DDF3E302A42A014CA25894100061C2E/$File/1686.1%20Final%20PSD%20-%20July%202023%20-%20Updated.pdf

In the partition state model (PSM) paradigm, responders are identified as being in progression-free survival (PFS), as opposed to the second of only two independent Kaplan-Meier (K-M) inputs – in overall survival (OS)[5]. As emphasised above, in the original model, only patients in the PFS health state received ^{177}Lu PSMA i&t treatment in each cycle, starting from the first. It also implies that the ^{177}Lu PSMA SPECT administered 24 hours after each of the 6-week cycles is used as a disease progression monitoring procedure as well as for clinical decision making, in particular, the decision to terminate treatment in non-responders. Indeed, the original MSAC 1686 ADAR stated "[i]t is expected that in Australian clinical practice, post-treatment SPECT/CT would inform early treatment cessation in those not deriving clinical benefit from ^{177}Lu PSMA treatment thereby preventing unnecessary treatment" (MSAC 1686 ADAR, p.102). Subsequently MSAC confirmed that SPECT/CT is currently being used in Australian clinical practice following ^{177}Lu PSMA i&t therapy as a baseline for future comparisons, to implement treatment holidays in exceptional responders (which reduces futile radiation exposure and saves these doses, restricted to a maximum of six cycles, for later) and to consider therapy change if there has been significant disease progression. Overall, MSAC considered it appropriate for an MBS item descriptor for the ^{177}Lu PSMA therapy to retain the proposed specification "followed 24 hours later by whole body Lu PSMA single-photon emission computed tomography (SPECT)" (MSAC 1686 PSD July 2022, p.5).

The proposed two-step treatment algorithm implies that prior to the assessment for response to treatment, all surviving patients receive at least two ^{177}Lu PSMA i&t doses. It means, that for the first 2 cycles, the cost per 6-week cycle ($8,000) should be assigned not to the proportion of patients in the PFS health state, but to the higher proportion of patients in the OS health state, thus increasing the overall cost of treatment. Since the MSAC 1686.1 resubmission ADAR did not make this amendment to the model, it was performed by the evaluators and reflected in the Commentary to the MSAC 1686.1 resubmission ADAR. The OS data for the first 12 weeks from the VISION trial was utilised in order to preserve the integrity of the model that was violated by using patient-level data from two different trials. In particular, the PFS data from the TheraP trial was used exclusively for calculating the cost of ^{177}Lu PSMA i&t treatment, while the health benefits and other treatment-related costs were informed by the data from the VISION trial.

To reiterate, to ensure consistency with the two-step approach to treatment, the evaluators have corrected the model in two ways, albeit simultaneously. Firstly, the unit cost of ^{177}Lu PSMA i&t treatment was applied to all surviving patients for the first 2 cycles. Secondly, OS data from the VISION trial was used to ensure, as stated above, that both costs and outcomes were sourced from a single trial. These corrections increased the ICER by 29% ($94,936 from $73,622 /QALY), making it a primary driver of the ICER estimate. The second-largest driver was the choice of treatment-specific, rather than health state-specific, utility values. Note, it was not necessary to change the "structure of the PSM" (in a way it would be evident in the context of a state-transition model, such as Markov) in order to incorporate the two-step approach into the model.

In considering the MSAC 1686.1 resubmission ADAR, MSAC again 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) was too high and uncertain (MSAC 1686.1 PSD July 2023, p.1). MSAC deferred its advice and requested that a revised economic evaluation be conducted (referred to as "terms of reference" for this fit-for-purpose Department Contracted Assessment Report (FFP DCAR)):

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[5] In PSM, the K-M data represent the proportions of PFS and OS at each observation point. The PFS and OS health state are structurally independent. The proportion of patients in the progressed disease state (PD) for each modelling cycle is not calculated using transition probabilities as in a state-transition model (e.g. Markov), but by deducting PFS from the OS (PD=OS-PFS).

- with the model structure corrected to capture the two-step approach to treatment (based on the Re-SPECT study) proposed in the MBS items for ^{177}Lu PSMA therapy;
- 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 1686.1 PSD July 2023, p.2). At the same time, although MSAC had a preference for a more conservative time horizon of 5 years, MSAC considered a 7.5-year time horizon would likely to be acceptable (MSAC 1686.1 PSD July 2023, p.6).

MSAC considered that the proposed changes to the model would allow a more accurate estimate for the ICER including whether ^{177}Lu PSMA i&t therapy was acceptably cost-effective at the proposed price of the therapy (MSAC 1686.1 PSD July 2023, p.7). It was also assumed that the FFP model would still rely on survival data from the VISION trial in tracing the progression of patients.

Table 1 summarises the key matters of concern. For completeness, the key features of the original model (MSAC 1686 ADAR) and the associated matters of concern were added to the table. In the original model and in the model developed for this FFP DCAR, health state allocation over time in ^{177}Lu PSMA i&t arm was determined by PFS and OS data sourced from VISION (Sartor et al. 2021[6]). The evaluators amended the original model (MSAC 1686 ADAR) with the updated prices of pharmaceuticals and health services and also included the subsequent MSAC recommendations about time horizon and utility values. However, in the original model only those remaining in the PFS health state continue to receive ^{177}Lu PSMA i&t treatment, while progressed patients receive an alternative treatment starting from the first cycle. This assumption is inconsistent with the two-step treatment algorithm requested in the terms of reference for the MSAC 1686.1 FFP DCAR.

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[6] Sartor O, De BonoJ, Chi K.N, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med, 2021; 385, 1091-1103.

Table 1   Summary of key matters of concern

Component	Matter of concern raised by MSAC in July 2022 in relation to 1686 ADAR (original submission)	Whether the FFP DCAR amendments addresses it	Matter of concern raised by MSAC in July 2023 in relation to 1686.1 ADAR (resubmission)	How the current FFP DCAR addresses it
Cost-effectiveness analysis (CEA)	MSAC accepted the high certainty from the evidence that ^{177}Lu PSMA i&t therapy is acceptably safe and effective, but that the ICER was too high and uncertain. MSAC noted that in the TheraP trial, patient reported outcomes and quality of life were better with ^{177}Lu PSMA-617 than cabazitaxel, suggesting that the utility of PFS should be higher with ^{177}Lu PSMA i&t than cabazitaxel. MSAC noted that… [t]he first driver was cabazitaxel OS, which the ADAR assumed to be the same as the OS hazard ratio (HR) of ^{177}Lu PSMA-617 versus best supportive care (HR=0.62). The second key driver was extrapolation, where the treatment effect continued beyond 20.9 months in the trial period for up to 10 years. The third key driver was the time horizon, which was 10 years in the base case. Weighted comparator included 75% cabazitaxel and 25% BSc.	The 0.04 disutility reflecting cabazitaxel toxicity was used in the CEA. Other utilities remained health state specific. The assumed HR for cabazitaxel OS (0.62) was replaced with the value (1.00) obtained from the latest data from TheraP provided during the pre-MSAC response. The time horizon in the base-case was 7.5 years consistent with previously considered for abiraterone, i.e. 7 years in duration (Abiraterone November 2012 PSD). Updated to weighted comparator of 75% BSc and 25% cabazitaxel consistent with that previously considered for olaparib in mCRPC (Olaparib PSD July 2021).	MSAC considered the ICER was too high and uncertain (PSD p2) and advised the applicant to consider how the ICER may be reduced… (PSD p6). The model structure should be corrected to capture the two-step approach to treatment (based on the Re-SPECT study). Better justification (or removal) of the selected treatment specific utility weights. Patient-level data from different trials should not be used in the same model.	The CEA is based on a hybrid model that explicitly incorporates the probability of response reported in the Re-SPECT study. Use of patient-level data from different trials was already corrected in the Commentary to the MSAC 1686.1 resubmission ADAR. Similarly, utility weights used in the model are treatment agnostic and health state-related.
Financial impact	The financial implications may be underestimated if the uptake rate is higher than assumed by the ADAR.	Additional assumptions about uptake rates were tested.	Updates to the financial impact based on the two-step approach to treatment.	The financial impact has been updated to reflect the two-step approach to treatment.

Abbreviations: BSc = best supportive care; CEA, cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; MBS, Medicare Benefits Schedule; MSAC, Medicare Benefits Advisory Committee; PSA, prostate specific antigen; PSD, public summary document
Source: MSAC 1686 PSD; MSAC 1686.1 PSD

5.   Prerequisites to implementation of any funding advice

Consistent with other radiopharmaceutical products for which the administration is funded through the MBS, the proposed therapeutic intervention ^{177}Lu-PSMA-i&t, is produced under Good Laboratory Practice (GLP) in Australia. GLP-compliant production of ^{177}Lu-PSMA-i&t is the current standard of care (SoC) for the provision of radiopharmaceutical treatments across Australia, within trials and clinically. It is routinely used in nuclear medicine departments for radio-pharmacy production across Australia. GLP production of ^{177}Lu-PSMA-i&t is currently available through the TGA exemption for production of radiopharmaceuticals in public or private hospitals for local use and not for on-sale.

6.   Proposal for public funding

The proposed item descriptor for PSMA PET is presented in Table 2. The item descriptor remains unchanged from that presented in the MSAC 1686 and MSAC 1686.1 PSDs, as does the requested fee. As noted in the commentary to the original ADAR (MSAC 1686), outpatient treatment is appropriate and currently in place with some providers, in these cases the greatest permissible gap (GPG; $98.70) would apply.

Table 2   Proposed item descriptor for PSMA PET

Category 5 - Diagnostic Imaging Services
MBS item XXXX
Whole body prostate specific membrane antigen (PSMA) positron emission tomography (PET) study, performed for the assessment of suitability for Lu*tetium 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. *(R) (Anaes)*
Fee: $1,300 Benefit: 85% = $1,201.30*

Source: Table 2, p9 of the MSAC 1686.1 PSD, July 2023
* 85% benefit reflects the 1 November 2023 Greatest Permissible Gap (GPG) of $98.70. All out-of-hospital Medicare services that have an MBS fee of $658.35 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

The proposed item descriptors for initial and continuing therapy with ^{177}Lu PSMA i&t in the MSAC 1686.1 resubmission ADAR (considered at the July 2023 MSAC meeting) are presented in Table 3 and Table 4, respectively. These are considered unchanged in this FFP DCAR.

The proposed fee for ^{177}Lu PSMA i&t remains unchanged from the previous ADARs at $8,000 per dose, which includes a whole body ^{177}Lu-PSMA single-photon emission computed tomography (SPECT) 24 hours following each treatment. As noted in the commentary to the previous ADARs, the patient contribution ($1,200) may be prohibitive for some patients. Outpatient treatment is appropriate and currently in place with some providers, in these cases the greatest permissible gap (GPG; $98.70) would apply.

Table 3   Proposed item descriptor for Lutetium 177 PSMA – initial phase

Category 3 - Therapeutic Procedures T3. Therapeutic Nuclear Medicine
MBS item ZZZZ Treatment phase: initial treatment Administration of Lutetium 177 PSMA followed 24 hours later by whole body Lu-PSMA single-photon emission computed tomography (SPECT) for treatment of a patient with metastatic castrate resistant prostate cancer, who is PSMA-positive as determined by PSMA PET defined as SUVmax >15 at a single site of disease and SUVmax >10 at all sites of measurable disease, after progressive disease has developed while on at least one taxane chemotherapy and at least one androgen receptor signalling inhibitor A patient is eligible to claim once per cycle up to a maximum of 2 cycles in the initial treatment phase.
Fee: $8,000 Benefit: 85% = $7,901.30*

Source: Table 3, p10 of the MSAC 1686.1 PSD, July 2023
*   85% benefit reflects the 1 November 2023 Greatest Permissible Gap (GPG) of $98.70. All out-of-hospital Medicare services that have an MBS fee of $658.35 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

The criteria for eligibility for initial treatment remains the same as that in the previous ADARs. Patients are required to be PSMA-positive as determined by PSMA PET defined as SUV_{max} >15 at a single site of disease and SUV_{max} >10 at all sites of measurable disease, after progressive disease has developed while on at least one taxane chemotherapy and at least one androgen receptor signalling inhibitor. The initial phase is limited to 2 cycles.

The item descriptor for continuing treatment was limited to those who do not develop disease progression while on treatment with ^{177}Lu PSMA i&t. Disease progression is defined as a rise in PSA of > 2 ng/mL confirmed by 2 tests a minimum 2 weeks apart or evidence of new soft tissue metastases on diagnostic CT as per RECIST criteria. The applicant subsequently proposed an amendment that disease progression would be defined in the item descriptor as an 'increase in serum PSA of at least 25% and at least 2 ng/mL after 12 weeks or evidence of new soft tissue metastases on diagnostic CT' (MSAC 1686.1 PSD July 2023, p.5).

As noted above, the resubmission ADAR proposed the initial phase of treatment constitutes at least 2 cycles of treatment before the assessment of response based on the results from the Re-SPECT study reported by Emmett et al (2023).

Table 4   Proposed item descriptor for Lutetium 177 PSMA – continuing phase

Category 3 - Therapeutic Procedures T3. Therapeutic Nuclear Medicine
MBS item YYYY
Treatment phase: continuing treatment
Administration of Lutetium 177 PSMA followed 24 hours later by whole body Lu-PSMA single-photon emission computed tomography (SPECT) for treatment of a patient with metastatic castrate resistant prostate cancer, if: • a service to which item ZZZZ has been provided; and • the patient must not have developed disease progression while receiving Lutetium 177 PSMA for this condition
Disease progression for the purposes of administering MBS item YYYY is defined as a rise in PSA of > 2 ng/mL confirmed by 2 tests a minimum 2 weeks apart and/or evidence of new soft tissue metastases on diagnostic CT as per RECIST criteria.
A patient is eligible to claim once per cycle up to a maximum of 4 cycles in the continuing treatment phase.
Fee: $8,000 Benefit: 85% = $7,901.30*

Source: Table 4, p11 of the MSAC 1686.1 PSD, July 2023
*   85% benefit reflects the 1 November 2023 Greatest Permissible Gap (GPG) of $98.70. All out-of-hospital Medicare services that have an MBS fee of $658.35 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

Effectively, with the introduction of the 2-step treatment algorithm, the research question is altered into the comparative effectiveness and cost-effectiveness analysis of the three alternative treatment strategies ((1) ^{177}Lu PSMA i&t for 6 cycles; (2) ^{177}Lu PSMA i&t for the first two cycles followed by an alternative treatment; and (3) current treatment – best supportive care : cabazitaxel). While the VISION and TheraP trials provide evidence on the first and the third treatment strategies, enrolling, due to their randomised nature, the same mCRPC populations in both arms of the trials, the population suggested for the second strategy is distinctly different from the population eligible for the first ^{177}Lu PSMA i&t strategy (as demonstrated by analysis of their baseline difference and clinical outcomes in Re-SPECT study). Although the K-M data is available for the ^{177}Lu PSMA i&t treatment strategies, there is no comparator evidence corresponding to the current treatment available to these subgroups of patients.

7. Population

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

Diagnostic test 1: PSMA PET/CT
If positive maximum standardised uptake value (SUV$_{max}$ of >15 at ≥1 disease site *AND* SUV$_{max}$ >10 at all measurable sites) and adequate marrow/liver/renal function, patients are then eligible for

Therapeutic intervention:
- [177]Lu PSMA i&t, 7.5-8.5 GBq IVI every 6 weeks for up to 2 cycles (initial)
- [177]Lu PSMA i&t, 7.5-8.5 GBq IVI every 6 weeks for up to 4 cycles (continuing; if have not developed disease progression while being treated with ^{177}Lu-PSMA)
- [177]Lu PSMA SPECT/CT 24 hours post-infusion for each cycle

The diagnostic test (PSMA PET/CT) will not replace any currently funded tests.

The intervention (^{177}Lu PSMA i&t) will replace or displace cabazitaxel and displace best supportive care.

8. Comparator

Diagnostic test: no testing with PSMA PET/CT

Therapy:
- cabazitaxel; or
- standard care if prior cabazitaxel, or unsuitable/unwilling for cabazitaxel.

9. Summary of public consultation input

The previous ADAR 1686.1 considered by MSAC in July 2023, received input from 11 organisations and three (3) consumer organisations (14 organisations in total): For further details see the 1686.1 Public Summary Document (pages 13-14).
Additional feedback was received for the current FFP DCAR 1686.1 from four organisations who previously provided input and one additional organisation, resulting in a total of 15 organisations (of which 5 were private companies and 3 consumer and patient advocacy organisations).

As with the previous feedback received, all consumer organisations and most other organisations were supportive of the application.

The benefits of the proposed medical service for patients were considered to include the following:

- Two organisations considered the proposed service would provide an alternative effective treatment, which is preferred by consumers due to poorly tolerated drug treatments. Additionally, one patient advocacy organisation highlighted the important quality of life benefits associated with the proposed treatment, including significantly less pain, fatigue and nausea; and also providing patients who have limited life expectancy a choice and a viable treatment option, that allows them to retain social functioning to spend quality time with their loved ones.
- One organisation stated it strongly supports the proposed two-step approach to treatment. Additionally, one specialist organisation considered this method has the advantage of selecting patients who will benefit from a full treatment course of 177-Lutetium PSMA therapy and avoids providing this therapy to patients unlikely to benefit.
- One specialist organisation also considered that public funding would make this treatment more accessible and affordable, which would provide more equitable access to this proven effective treatment.

The concerns raised in the consultation feedback for the proposed intervention included:

- One commercial organisation raised several issues with the application:
  - The organisation reiterated a previous submission that there was insufficient evidence to support the therapeutic equivalence between [177]LuPSMA i&t and ^{177}Lu PSMA-617, and that the limited body of available data does not allow for a reliable clinical comparison between the two structurally different products.
  - Additionally, it was highlighted that the proposed treatment regimen is different from the treatment sequencing used in trials involving [177]LuPSMA i&t (and also different from treatment sequencing in the VISION trial, which was investigating ^{177}Lu PSMA-617). The organisation said that these differences increased uncertainty in the economic analysis submitted in connection with the application, and brought into question the cost effectiveness analysis concerning [177]LuPSMA i&t.
  - The organisation provided legal correspondence between it and the applicants revealing a dispute over patent issues associated with the proposed use of [177]LuPSMA i&t in Australia. There was no indication that there have been any court rulings about the patent issues or that the patent dispute is currently the subject of any legal proceeding. The organisation referred to two patents which it stated "are both valid and enforceable, and are or may be relevant to the applicants' proposed exploitation of 177LuPSMA i&t as contemplated by the Application." The organisation stated that this is an issue that MSAC should take into account, particularly given its potential impact on patients. The organisation stated that it had applied to the Therapeutic Goods Administration for regulatory approval of ^{177}Lu PSMA-617.
- One organisation raised concerns that the proposed accreditation requirements are restrictive and not clinically appropriate. Additionally, the organisation raised concern that the proposed fee will make Lutetium PSMA unviable in most settings.

Other comments raised regarding the proposed interventions were:

- Three organisations supported the proposed service fee. In addition, one highlighted that the proposed service fee is significantly lower than the private patient cost for the same medical service (between AUD 12,000 to 30,000).

10. Characteristics of the evidence base

Table 5 presents a summary of the key features of the new evidence included in resubmission.

Table 5   Key features of the new evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias	Use in modelled evaluation
OS from TheraP	Presentation from 2022 ASCO Annual meeting (Hofman et al.2022)[7]	n=200	High	HR values were updated using 3-year data from TheraP trial
Re-SPECT study (Emmett, 2023) demonstrated that the patients in progressed disease health state after 2 cycles do not achieve any health benefits with the subsequent ^{177}Lu PSMA treatment. This result justified a 2-step treatment algorithm	Emmett et al., 2023	n=125 (n=116 used to calculate probabilities of response)	High	As in the MSAC 1686 ADAR, health state allocation over time determined by PFS and OS data. PFS and OS data for ^{177}Lu PSMA were sourced from VISION (Sartor et al. (2021a)). In the hybrid model, the original K-M observations from the VISION trial (Sartor 2021) and the corresponding parametric extensions were split into "responders" and "non-responders" in proportions informed by the Re-SPECT study (Emmett, 2023). Only responders continue to receive ^{177}Lu PSMA treatment after the first 2 cycles.

OS overall survival, HR= Hazard Ratio, n = number of patients, ASCO American Society of Clinical oncology.

MSAC approved the algorithm, where the initial phase of treatment constitutes at least 2 cycles of treatment before the assessment of response based on the results from Emmett al (2023) (the Re-SPECT study, a retrospective analysis of a clinical ^{177}Lu PSMA i&t treatment program, n= 125).

The Re-SPECT study was a retrospective analysis of a clinical ^{177}Lu PSMA i&t treatment program. It included 125 men who underwent ^{177}Lu PSMA i&t therapy between May 2019-April 2022. Following dose 2 (week-6), a composite prostate serum antigen (PSA) and ^{177}Lu SPECT/CT imaging response (partial response (PR), stable disease (SD) and progressive disease (PD)) determined ongoing management. Implicitly, SPECT/CT, which is a part of the procedure and costed as such, is assumed to be the way of identifying disease progression (as opposed to merely establishing and categorising the response).

In Re-SPECT, all men had mCRPC (SUV$_{max}$ >15 on PSMA PET at ≥1 site, and SUV$_{max}$ >10 at all measurable sites, consistent with the intended population), 99% (124/125) had prior ASI and 70% (88/125) prior docetaxel. This differs to the intended population who are required to have "progressive disease … while on at least one taxane chemotherapy and at least one androgen receptor signalling inhibitor". Of those categorised in response group 1 (RG1), RG2 and RG3, 51% (21/41), 82% (32/39) and 78% (28/36) men respectively had received prior chemotherapy.

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[7] Hofman MS, Emmett L, Sandhu S, et al. TheraP: 177 Lu-PSMA-617 (LuPSMA) vs. cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel – overall survival after median followup of 3 years (ANZUP 1603) J Clin Oncol. 2022;40:5000

Mean age was 75 years (70-80). Patients received a median of 3 doses up to a maximum of 10 (IQR 2-4). Six per cent (9/125) had been previously treated on a clinical trial with ^{177}Lu PSMA 617. Overall, 60% (75/125) had a PSA reduction >50% (PSARR). At the time of analysis 42% (52/125) were deceased. In the overall study population, the median PSA-PFS was 6.1 months (95% CI: 5.4-6.7) and OS 16.8 months (95% CI: 13.5-20.1).

Patients were assigned to response groups (see Table 6 for definitions), a "rise" in PSA, used to categorise response group 3, was not defined. The proportion of patients in each of the response groups is also reported in Table 6. There was a significant difference in PSA-PFS and OS between response groups (see Table 6), p <0.0001 and p<0.0005, respectively. Similarly, PSA50% (prostate serum antigen reduction of at least 50%) was also significantly different between response groups (see Table 6, p<0.0001).

Table 6   Response group categorisations and the results reported in Re-SPECT study (Emmett, 2023)

Response group	N=116 (those assigned to a response groups)
1. Marked reduction (50%) in PSA and imaging-PR break in treatment until subsequent PSA rise, then consider re-treatment. Imaging PR (partial response) was classified as a significant response on imaging (between baseline and week-6 Lu-SPECT/CT) defined as a marked reduction (>30%) in visual tumour volume at all sites of involved disease, no new sites of PSMA avid tumour deposits and no new sites of PSMA negative tumour deposits on diagnostic CT.	41 (35%) PSA-PFS median 12.1 (95% CI: 9.3-17.4) months OS median 19.2 (95% CI: 16.8-20.7) months PSA50% RR: 93% Median 3 (IQR 2-4) doses of 177LuPSMA-I&T All men had a treatment break due to significant treatment response, with a median 6.1 months (IQR 3.4-8.7) of treatment 'holiday' prior to a subsequent rise in PSA and consideration for re-treatment.
2. Stable or reduced PSA (<50%) and/or imaging SD) ongoing 6 weekly treatments until 6 doses, or no longer clinically benefitting. Stable disease (SD) was classified as no visible marked change in tumour volume (>30%), no new sites of PSMA avid disease on diagnostic CT (imaging PD).	39 (34%) PSA-PFS median 6.1 (95% CI: 5.8-9.0) months OS median 13.2 (95% CI: 12.0-18.8) months PSA50% RR: 74% Median 4 doses (IQR 3-5) 177LuPSMA-I&T
3. Rise in PSA and/or imaging PD consider referral to an alternative treatment. Progressive disease was defined as visual increase in tumour volume (>30%) ± new sites of disease and/or the presence of new sites of PSMA-negative disease progression on diagnostic CT (imaging PD).	36 (31%) assumed to be "non-responders" PSA-PFS median 2.6 (95% CI: 1.6-3.1) months OS median 11.2 (95% CI: 8.7-15.6) months PSA50% RR: 8% Median 3 (IQR 2-3) doses 177LuPSMA-I&T. A PSA rise occurred in 92% (33/36) prior to cycle 3. Which is equivalent to 33/116=28.4% of patients who would not have met the proposed continuation criteria

IQR = interquartile range; PD = progressive disease; PFS = progression-free survival; PR = partial response; PSA = prostate serum

Given 31% of patients enrolled in Re-SPECT failed to respond to treatment, it is possible that the nominated eligibility criteria (SUV_{max} >15 on PSMA PET at ≥1 site, and SUV_{max} >10 at all measurable sites), may not be 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.

Figure 1 presents the (a) PSA-PFS and (b) OS for the three response groups in the Re-SPECT study.
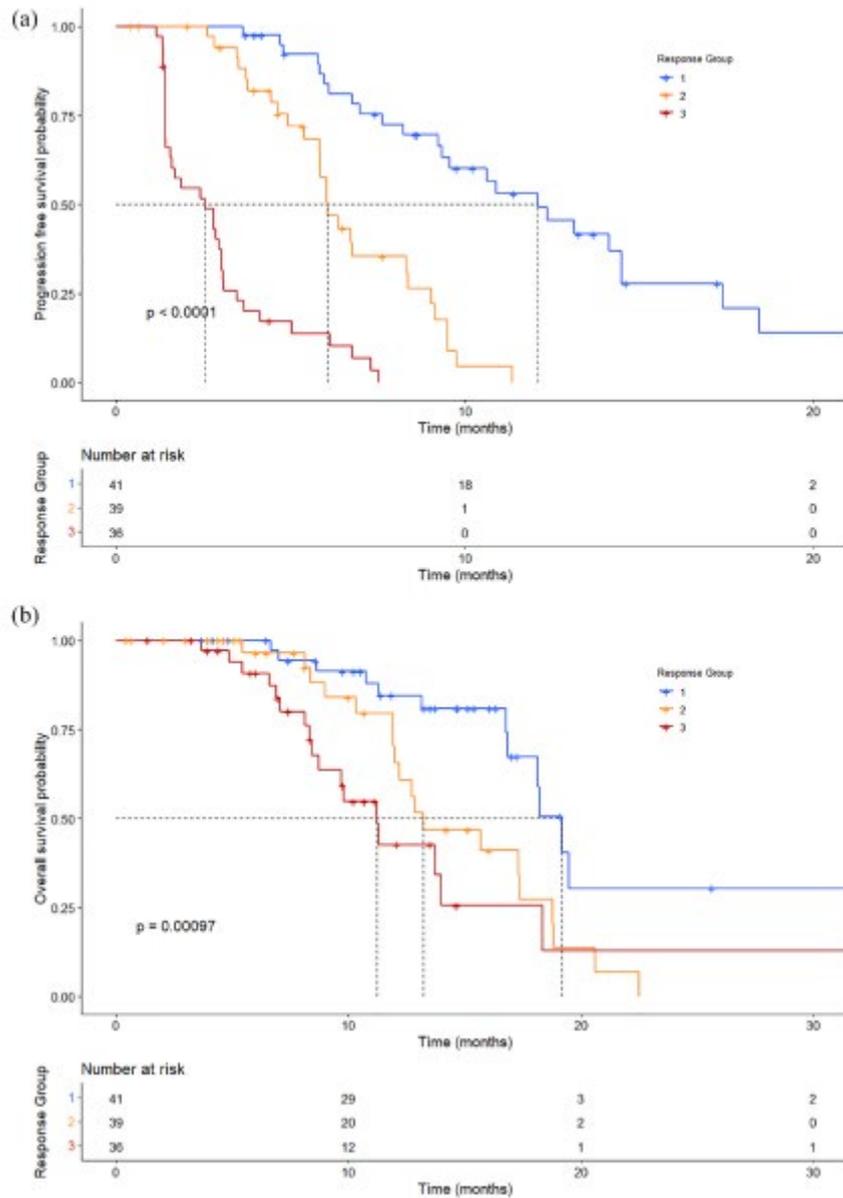
Figure 1   Kaplan–Meier curve for (a) PSA-PFS in patients with marked reduction in PSA and imaging PR (blue) versus stable or reduced PSA and/or imaging SD (yellow) and rise in PSA and/or imaging PD (red) and (b) demonstrating OS in the same cohorts.
Source: Figure 1, p5 of Emmet et al (2023)
OS, overall survival; PD, progressive disease; PFS, progression-free survival; PSA, prostate-specific antigen; SD, stable disease.

11.   Comparative safety

The comparative safety was not reconsidered in this FFP DCAR. MSAC accepted the high certainty from the evidence that ^{177}Lu-PSMA i&t therapy is acceptably safe.

12. Comparative effectiveness

The comparative effectiveness was not reconsidered in this FFP DCAR. MSAC accepted the high certainty from the evidence that ^{177}Lu-PSMA i&t therapy is acceptably effective.

There is insufficient evidence to address the re-formulated research question (as stated above): of comparative effectiveness and cost-effectiveness analysis of the three alternative treatment strategies ((1) ^{177}Lu PSMA i&t for 6 cycles; (2) ^{177}Lu PSMA i&t for the first two cycles followed by an alternative treatment; and (3) current treatment – best supportive care:cabazitaxel).

13. Economic evaluation

The "hybrid model" was specifically designed to address the MSAC's request. MSAC considered that the two-step approach to treatment whereby treatment is split into initial (up to 2 cycles) and continuing treatment (3-6 cycles) was appropriate but that the model structure used in the economic evaluation did not capture each step separately (MSAC 1686.1 PSD, p.5). MSAC considered any revised model should capture the difference in probability of response in the first 2 cycles over the following 4 cycles as demonstrated in the Re-SPECT study (MSAC 1686.1 PSD, p.5). In addition, MSAC requested better justification (or removal) of the selected treatment specific utility weights (MSAC 1686.1 PSD, p.7). At the same time, although MSAC had a preference for a more conservative time horizon of 5 years, MSAC considered a 7.5 year time horizon was acceptable (MSAC 1686.1 PSD, p.6).

The conceptual differences between a state-transition model and partition-survival models (PSM) may have been underestimated. In the state-transition paradigm, a state membership is determined by applying a set of transition probabilities that an individual currently in one health state will move to another state in the following cycle. The complete set of such probabilities could not be extracted from the Re-SPECT study. At best, there is a single point-in time conditional probability of a response after the second cycle. The response group-specific probabilities of getting to this point are not available, since, apart from identifying the proportion of non-responders, the Re-SPECT study chose the K-M format for data collection with the corresponding graphical representation of PFS and OS curves.

Unlike the state-transition model, in the PSM paradigm the differences in state membership are determined by their survival curves (i.e. their shape and slope). The OS and PFS curves are structurally independent, i.e. each end point is independently modelled (using the original time-to-event K-M data) and for each arm of the model the estimates of both PFS and OS are required. In PSM health benefits and costs are estimated by calculating the area under the curve (the proportions of PFS or OS patients multiplied by the cycle length and aggregated), unlike in Markov model that counts cycles spent in one or another health state.

In state-transition modelling the health states must be mutually exclusive and exhaustive, therefore transition probabilities of moving from one state to all other states must sum to 1. The same condition also applies in PSM, which follows a cohort of patients through time as they move between a set of exhaustive and mutually exclusive heath states. The proportions of being in each health state must sum to 1 for each treatment strategy in each cycle. It will be demonstrated below that in the absence of data to populate the hybrid model, a set of assumptions had to be made and it resulted in violation of this fundamental condition.

During consultation with the department, it was suggested that a decision tree (i.e. a state-transition model) that would depict patients' progression up to the assessment of response at

week 6 and classify them by response to treatment (as in Re-SPECT study), could be linked to the PSM model informed by the VISION trial data. An *ad hoc* literature search was undertaken in an attempt to find such a "hybrid" model that would transition patients from a decision tree to PSM. The results of the literature search failed to identify such a model, but it was confirmed that in many instances, external data are only available for the PFS and OS endpoints. These data are not sufficient to allow estimation of individual transition probabilities because PFS describes the combination of progressions (PD) and deaths from the progression-free state and OS describes the overall probability of death, which is a function of all three transition probabilities. Also, whenever the time-to-progression was estimated with respect to response, it was modelled using separate parametric curves by treatment and response category. While the survival curves for patients from every response group are provided by Emmett (2023), but in the absence of a comparator – current treatment, could not be utilised. The PFS and OS curves from the VISION RCT are not available with respect to "response" status, whether after the 4 cycles of ^{177}Lu PSMA i&t when the patients were assessed for disease progression in this study or after the first 2 cycles as suggested by the 2-step treatment algorithm.

The evaluators have concluded that, setting aside the questionable utilisation of the observations from two distinctly different studies, there are insufficient time-to-event data to merge the decision tree, based on the incomplete (for the modelling purposes) Re-SPECT study with PSM (based on VISION) without a serious violation of the underlying assumptions of either the state-transition or PSM paradigms, or both.

Nevertheless, in order to meet the terms of reference for the FFP DCAR, the following hybrid model was constructed (Figure 2).
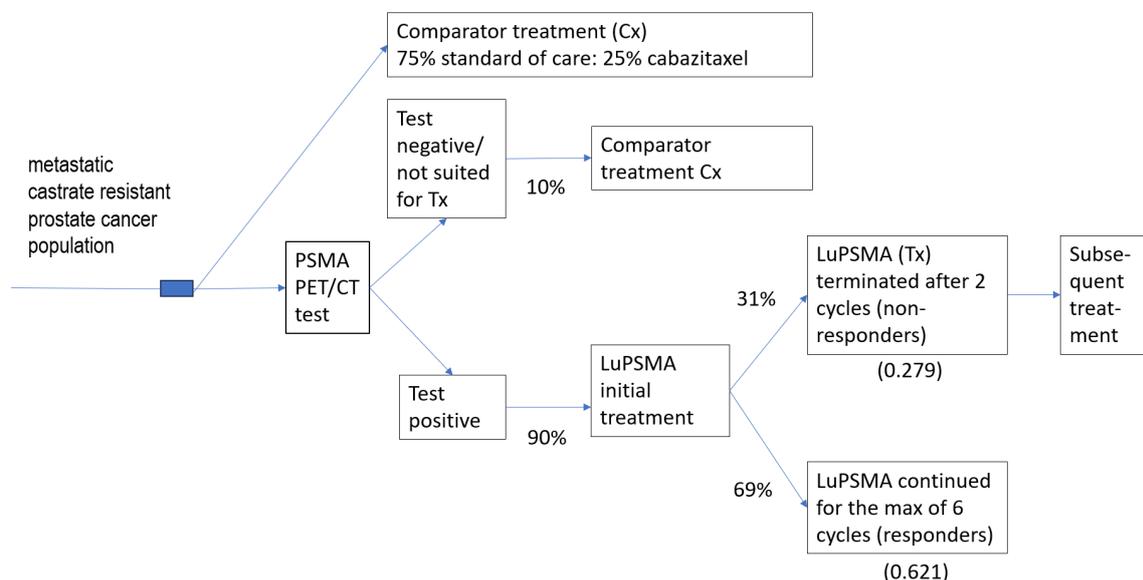
Figure 2 Schematic presentation of a hybrid model of ^{177}Lu PSMA i&t treatment in mCRPC population

As in the ADAR models, eligibility for ^{177}Lu PSMA i&t treatment is established with PSMA PET/CT investigation (MBS item for the proposed diagnostic imaging). The proportion of patients (by definition, all surviving patients) who were found suitable for the treatment (90%, using TheraP finding) initiate ^{177}Lu PSMA i&t in week 0 and, after receiving 2 cycles (week 6), undergo a composite (PSA + SPECT/CT) assessment to establish response to treatment. Patients with

response continue receiving ^{177}Lu PSMA i&t treatment for the next 4 cycles (up to the maximum of 6 cycles), while non-responders will be recommended for an alternative treatment.

It was assumed that 'responders' progression through health states could be approximated by the ^{177}Lu PSMA arm of the VISION trial, while 'non-responder' progression could be modelled using the comparator arm (75% best supportive care:25% cabazitaxel). In practical terms, the K-M/parametric survival data were split in a proportion of 69% to 31%, where the observed proportions of patients in PFS and OS health states in the ^{177}Lu PSMA arm of the VISION trial were adjusted by the coefficient of 0.621 (0.69*0.9) to represent the 'responders' progression through the health states. All surviving responders attracted the ^{177}Lu PSMA i&t treatment cost for the full 6 cycles. Although the Re-SPECT study reported that all patients in RG1 had a treatment break due to significant treatment response, with a median 6.1 months (IQR 3.4-8.7) of treatment 'holiday' prior to a subsequent rise in PSA and consideration for re-treatment and not all opted to return for further treatment, this was considered to be largely based on financial reasons (communication with the applicant), a constraint that would no longer be relevant should ^{177}Lu PSMA i&t be listed on the MBS. Thus, all PFS patients were assumed to undertake all 6 cycles of treatment. To estimate costs and health gains of 'non-responders', the K-M/parametric survival data in the comparator arm were adjusted by the coefficient of 0.279 (0.31*0.9). The Lu PSMA i&t treatment cost applied for the first 2 cycles followed by the post-discontinuation costs as that would apply to ^{177}Lu PSMA i&t patients (a proportion of these patients would receive cabazitaxel). The original estimates of costs and health gains of the patients in the comparator arm were not affected. The comparator data was used merely as a substitute for the non-existing survival data for 'non-responders'.

It should be noted that the amended model now represents not two, but three treatment strategies, each with its distinct characteristics of transitioning patients through time (whether dictated by the time-to-event data or transition probabilities).

This approach violates the PSM assumption that the proportions of patients being in each health state (from the mutually exclusive and exhausted set) must sum to 1 for each treatment strategy in each cycle. In particular, it is very likely that the probability of death differs between "responders" and "non-responders", however, since the OS is altered by the need to apply proportions, reflecting the assessment outcomes after the second cycle, the conventional way of determining a proportion of dead in each cycle does not apply.

For example, in the first cycle only 62.1% of Lu PSMA i&t patients in the response group are alive, and since they are all responders, the same proportion is in the PFS health state. The number of progressed responders is zero (PD=OS-PFS), but how many are in the "death state" cannot be derived with certainty, since it would be unreasonable to apply the conventional rule of (1-OS) that would produce the rate of death at 37.9%. Evidently, the proportion of 'non-responders' (a complement to the 62.1% is 27.9%) is alive at first and is following the second Lu PSMA i&t treatment strategy, approximated by the VISION data for the comparator. However, in the comparator arm all the patients are assumed to be identical to the VISION patients from Lu PSMA arm at baseline. The rates of their progression to death in each cycle is therefore determined by the differences in effectiveness of the intervention and the comparator. This is not the case with respect to progression of non-responders who are different at baseline from responders and, since there is no response-related evidence for the comparator arm, it is impossible to estimate an accurate rate of progression to "death" that would be specific to non-responders.

Since we were unable to identify a precedence of a similar hybrid model in the literature, the degree to which the violation of the assumption of proportions of patients totalling to one in each cycle invalidates the modelled outcomes is unknown.

The key components of the economic evaluation is presented in Table 7 and a high-level summary of the input data used in the model and their sources is provided in Table 8.

Table 7   Key components of the economic evaluation

Perspective	Australian healthcare system
Population	Patients with mCRPC who have received at least one ASI (i.e. abiraterone, enzalutamide or darolutamide via PBS/RPBS) as well as at least one line of chemotherapy (docetaxel +/- cabazitaxel via PBS/RPBS) in the setting of mCRPC
Prior testing	PSMA PET/CT
Patient pathway	Only patients who have not developed disease progression after receiving ^{1177}Lu PSMA i&t: in the first two cycles are eligible to continue the treatment for up to 6 cycles.
Comparator	Base-case: weighted comparator of 75% BSc and 25% cabazitaxel was made consistent with that previously considered for olaparib in mCRPC (olaparib PSD July 2021).
Type(s) of analysis	Cost-effectiveness analysis, and cost-utility analysis
Outcomes	Cost per life-year gained (cost/LYG) Cost per quality-adjusted life year (cost/QALY)
Time horizon	7.5 years in the base-case, time horizon of 5 years in sensitivity analysis
Computational method	A hybrid model was developed where the PFS and OS data from VISION trial was apportioned to reflect the proportion of responders in Re-SPECT study
Generation of the base case	Outcomes of PFS and OS for ^{177}Lu PSMA i&t: were sourced directly from the ^{177}Lu PSMA 617 KM (ITT) data from VISION (Sartor, 2021a). Parametric functions were fitted to ^{177}Lu PSMA 617 KM data (from t=0) to extrapolate PFS and OS. To model ^{177}Lu PSMA i&t: outcomes: PFS and OS KM data for ^{177}Lu PSMA 617 was used until 20.9 months (median follow-up of VISION as reported in Sartor (2021a)). Beyond 20.9 months, parametric functions were used. The selection of parametric extrapolation was based on goodness-of-fit and clinical plausibility (as per ADARs). To model cabazitaxel/BSc outcomes: Proportional hazards approach was adopted whereby hazard ratios for PFS and OS from TheraP and VISION (Hofman 2021[8], Sartor, 2021a) were applied to the modelled PFS and OS in the ^{177}Lu PSMA i&t.
Health states	Three health states: progression-free survival, progressed disease and death
Cycle length	1 week
Patients' transition though health states	Health state allocation over time determined by PFS and OS data. PFS and OS data for ^{177}Lu PSMA i&t: were sourced from VISION representing a median follow-up of 20.9 months. transitions for the second ^{177}Lu PSMA i&t treatment strategy is derived from PFS and OS comparator data
Costs	Updated to January 2023 costs
Discount rate	5% for both costs and outcomes
Software	Microsoft Excel

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[8] Hofman MS, Emmett L, Sandhu 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

Table 8   Summary of the inputs used in the economic evaluation

Parameter	Value	Source
Efficacy inputs (PFS, OS)	For ^{177}Lu PSMA i&t: Informed directly from the ^{177}Lu-PSMA-617 + BSc arm of VISION. K-M data is used for the trial period followed by parametric extrapolation. For cabazitaxel/BSc: Proportional hazards approach was adopted. Specifically, HRs from TheraP and VISION (Hofman et al., 2021, Sartor et al., 2021) were applied to the OS and PFS K-M data and parametric extrapolation of the [177]LuPSMA arm.	Hofman et al. (2021), Sartor et al. (2021).
Safety inputs	Grade 3/4 AEs occurring in ≥5% of patients in TheraP and VISION.	Hofman et al. (2021), Sartor et al. (2021).
Proportion of patients eligible for ^{177}Lu PSMA i&t	90.0%	PSMA PET/CT screening data from TheraP.
Proportions of "responders" and "non-responders"	Responders (after the second dose, 6-week assessment) =69% Non-Responders=31%	Emmett (2023)
Health outcomes		
Health state utility values	Utility values. • PFS – 0.74 (Lu PSMA i&t and BSc) • PFS -0.70 (Cabazitaxel) • PD – 0.59	Magnus et al. (2019), originally sourced from Torvinen et al. (2013). 0.04 disutility reflects toxicity of cabazitaxel (Diels, 2015).
Disutility due to Grade 3/4 AEs	Various	Values and duration informed by NICE TA391 (National Institute For Health and Care Excellence (NICE), 2016)
Costs		
Cost of index treatments	[177]Lu PSMA i&t - $8,000/dose/$1,333.33 per week Cabazitaxel – $307.94/3-weekly cycle $141.57 per week (includes prednisolone and cost of administration) (as of 1 November 2023) BSc – assumed no cost	[177]Lu PSMA i&t (Includes the cost of SPECT/CT 24 hours later) - applicant Cabazitaxel – PBS, MBS BSc – assumption
Cost of subsequent treatment	Only subsequent cabazitaxel treatment was considered in this economic evaluation. 18% of those who progress following ^{177}Lu PSMA i&t treatment are assumed to receive subsequent cabazitaxel treatment. Total adjusted subsequent cabazitaxel treatment cost: $458.69 (includes prednisolone and cost of administration) No subsequent treatment costs were modelled following cabazitaxel	TheraP (Hofman et al., 2021) Cabazitaxel – PBS, MBS BSc – assumption
Healthcare resource utilisation	Resource use and frequency of use informed by local clinical experts. Resource use was mapped to the appropriate MBS item.	Local expert advice, MBS
Cost of terminal care	$41,569.18	Langton et al. (2016), inflated to 2023 AUD

Abbreviations: [177]Lu, lutetium-177; ABS, Australian Bureau of Statistics; AE, adverse event; AR-DRG, Australian Refined Diagnostic Related Group; AUD, Australian dollar; BSc, best supportive care; HR, hazard ratio; i&t, imaging and therapy; MBS, Medicare Benefits Scheme; NICE, National Institute for Health and Care Excellence; PBS, Pharmaceutical Benefits Scheme; PD, progressed disease; PFS, progression-free survival; PSMA, prostate specific membrane antigen; OS, overall survival; TA, technology appraisal; ToT, time on treatment

Table 9 shows results of a modelled economic evaluation economic evaluation.

Table 9 Stepped derivation of the base-case economic evaluation (discounted at 5%)

Strategy	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER
Step 1 (**cost per LY** – 7.5-year time horizon)					
[177]Lu PSMA i&t (responders)	*$55,077*		*1.05*		
[177]Lu PSMA i&t (non-responders)	*$15,480*		*0.35*		
10% allocated to comparator	*$4,443*		*0.124*		
Total ^{177}Lu PSMA i&t treatment strategy	**$75,000**	**$31,946**	**1.521**	**0.277**	**$115,500**
Total Cabazitaxel/BSc	**$43,055**		**1.245**		
Step 2 (**cost per QALY** – 7.5-year time horizon)					
[177]Lu PSMA i&t (responders)	*$55,077*		*0.70*		
[177]Lu PSMA i&t (non-responders)	*$15,480*		*0.22*		
10% allocated to comparator	*$4,443*		*0.08*		
Total ^{177}Lu PSMA i&t treatment strategy	**$75,000**	**$31,946**	**1.01**	**0.208**	**$153,583**
Total Cabazitaxel/BSc	**$43,055**		**0.80**		

Abbreviations: BSc, best supportive care; ICER, incremental cost-effectiveness ratio; ^{177}Lu, lutetium-177; LY, life-year; PSMA, prostate specific membrane antigen; QALY, quality-adjusted life year

The base-case ICER for ^{177}Lu PSMA i&t strategy compared with cabazitaxel/best supportive care is $115,500/LYG and $153,583/QALY.

A set of alternative models (historic base-cases) was reconstructed in order to trace down the disconnect between the proposed treatment algorithms and the modelling assumptions, see Table 10. The current prices of pharmaceutical were included to eliminate the changes in ICER due to the consecutive reductions in the cost of comparator cabazitaxel. Prices of other healthcare costs, including the cost of terminal care, were updated to 2023. The time horizon was set at 7.5 years, according to the MSAC's most recent advice (MSAC 1686.1 PSD July 2023, p.6), rather than the more conservative 5 years recommended by MSAC previously (MSAC 1686 PSD July 2022, p.5). Utility values were also replicated from the MSAC 1686.1 resubmission ADAR, as approved by MSAC (i.e. defined by health-state, treatment-agnostic, which still allows for a disutility to reflect cabazitaxel toxicity). The best supportive care:cabazitaxel split (essential for HR estimates) was 75%:25%. The Hazard Ratios used to estimate clinical effectiveness of the comparator cabazitaxel were updated to reflect the latest 3-year data from the TheraP trial (Hofman, 2022). A comparison of results across the historic models demonstrates the difference in the modelling assumptions about the rules for ^{177}Lu PSMA i&t treatment discontinuation and the approach to treatment cost calculation.

Table 10 A set of base-case analyses with alternative estimates of incremental costs and effectiveness (QALYs)

Strategy	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER ($/QALY)
Original model (MSAC 1686): treatment discontinuation at a weekly cycle*, SPECT/CT implicitly used for disease progression monitoring and clinical decision making (i.e. treatment termination in non-responders					
[177]Lu PSMA i&t	**$75,711**		**1.101**		
Cabazitaxel/BSc	**$42,996**	**$32,715**	**0.800**	**0.301**	**$108,743**
Resubmission 1686.1: a 2-step model: weekly discontinuation, SPECT/CT implicitly used for progression monitoring, except for the first 2 cycles when all surviving patients receive ^{177}Lu PSMA i&t^					
[177]Lu PSMA i&t	$76,263		1.101		
Cabazitaxel/BSc	$43,055	$45,727	0.800	0.301	$110,383[#]
FFP hybrid 2-step model: all LuPSMA-eligible patients are allocated into responders and non-responders groups after the second cycle (non-response is defined as a rise in PSA of >2 ng/mL and/or evidence of progression on diagnostic CT)					
[177]Lu PSMA i&t	$75,000		1.01		
Cabazitaxel/BSc	$43,055	$31,946	0.80	0.208	$153,583

*Although the health state benefit is affected by the choice of the cycle length, the number of patients who receive treatment in each cycle is not (it is a linear transformation).
^Cost of the first 2 cycles of LuPSMA treatment was assigned to all surviving patients by the evaluators (1686.1 Commentary model)
Abbreviations: BSc, best supportive care; i&t, imaging and therapy; ICER, incremental cost-effectiveness ratio; ^{177}Lu, lutetium-177; PSMA, prostate specific membrane antigen; QALY, quality-adjusted life year

[#]Please note the Addendum corrected an error with the previous ICER value reported. The error was in relation to how treatment was applied to surviving patients rather than those in PFS. The corrected ICER value in the base case model is $110,383/QALY instead of $151,993/QALY presented in the ffp DCAR.

Overall, the evaluators consider that the results of the original PSM model (presented in the MSAC 1686 ADAR) represents the most 'reliable' estimate of the ICER, due to the estimate relying solely on the VISION trial data for PFS and OS, (i.e. excluding the problematic use of patient-level data from different trials for determination of PFS benefits and costs in PSM model) and where time on treatment was based on only those remaining in PFS in VISION continuing treatment After the necessary price update and other MSAC-recommended amendments (time horizon of 7.5 years, health state specific utility values that still allow for disutility reflecting cabazitaxel toxicity) this resulted in a base case ICER of $108,743/QALY.
The applicability of the results to Australian clinical practice would depend on whether SPECT/CT assessment conducted after each cycle would be acceptable for both, disease progression monitoring and clinical decision making, in particular, the decision to terminate treatment in non-responders, starting from the first cycle. If positive, this would become inconsistent with two-step clinical algorithm currently reflected in the proposed MBS item descriptions.

Comparing results from the set of the models produced over the ADAR process indicates that, notwithstanding the methodological problems associated with the hybrid model designed for the FFP DCAR, the ICER from the resubmission ADAR (after all identified issues were addressed) is not much different from the ICER calculated in the hybrid model. However, the lowest ICER belongs to the original model with its implicit assumption that only the patients, who remain in the progression-free state receive treatment, beginning from cycle one. The difference is explained by the cost of treatment that in the 2-step models is assigned to non-responders in the first 2 cycles. Although there is a disconnect between the weekly cycle, which does not reflect clinical practice, and the SPECT/CT assessment conducted after every 6 weeks, the cost calculations are not affected by a weekly cycle.

Sensitivity analyses were undertaken, see Table 11, although the assumptions of the hybrid model generated a new source of a conceptual uncertainty that could not be addressed by means of varying the values of the parameters.

Table 11 Results of the scenario and sensitivity analyses

	Incremental cost	Incremental QALYs	ICER	Impact
Base-case	**$31,946**	**0.2080**	**$153,583**	N/a
Modelling assumptions Proportion of "responders" (69% 95%CI 0.60-0.77)				
Decreasing the 69% proportion using the lower 95%CI limit	$29,600	0.1812	$163,337	+6.4%
Increasing the 69% proportion using the upper 95%CI limit	$34,031	0.2318	$146,805	+4.4%
Discount rate 0% for costs and outcomes	$32,712	0.2359	$138,664	-10.0%
Discount rate 3.5% for costs and outcomes	$32,160	0.2157	$149,098	-2.9%
Time horizon of 5 years	$31,491	0.1844	$170,769	+11.2%
Comparator				
Assume 75% cabazitaxel, 25% BSc	$29,999	0.1159	$258,916	**+68.6%**
Assume 100% BSc	$32,850	0.2408	$136,424	**-11.2%**
Historic cost of cabazitaxel (February 2022) $1,068.78	$31,421	0.2080	$151,062	-1.6%
Utilities				
15D utility values from Torvinen et al. (2013) (PFS: 0.80, PD: 0.67)	$31,946	0.2203	$145,031	-5.6%
PFS: 0.86 (Krahn et al., 2007), PD: 0.635 (Wu et al., 2007) both sourced from Magnus et al. (2019)	$31,946	0.2371	$134,724	-12.3%
Utility cabazitaxel = 0.7 and BSc = 0.7 for PFS health state	$31,946	0.2208	$144,662	-5.8%
Costs				
Decrease terminal care costs ($41,569) by 20%	$31,728	0.2080	$152,635	-0.6%
Increase terminal care costs by 20%	$32,143	0.2080	$154,532	0.6%

Bold refers to changes +/- 15% to base-case ICER

Abbreviations: AE, adverse event; BSc, best supportive care; CI, confidence interval; CT, computerised tomography; FDG, fluorodeoxyglucose; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ^{177}Lu, lutetium-177; MSAC, Medicare Services Advisory Committee; OS, overall survival; PD, progressed disease; PET, Positron Emission Tomography; PFS, progression-free survival; PSMA, prostate specific membrane antigen; QALY, quality-adjusted life year; RD, risk difference

The results were robust with respect to almost all modelling assumptions and variations in parameter values. The only primary driver of cost effectiveness in the model was the assumption about the allocation of patients in the comparator arm to cabazitaxel and best supportive care. Reversing the baseline proportions of 25%:75% to cabazitaxel and best supportive care respectively into 75%:25%, increased the ICER by 68.6%. While the cost has marginally decreased, there was a disproportionate loss in health-related utility. The Commentary to the MSAC ADAR already detected the high degree of sensitivity of the modelled results to both, the variations in hazard ratios and the best supportive care:cabazitaxel split. The mathematics of the model (whether the original or the subsequent ones) includes hazard ratios in assigning the differential health benefit to the comparator arm. That is, proportions in PFS and OS health states in each cycle in the comparator arm are the PFS and OS proportions in the ^{177}Lu PSMA i&t arm raised to a degree set equal to the corresponding HR (2.28 and 1.46 for PSF and OS respectively). However, the HR values are derived using the best supportive care:cabazitaxel split (75%:25% in the base case). Therefore, results in the comparator arm, depend on the split a) directly as all costs are adjusted according to the proportion of patients treated with cabazitaxel

and b) indirectly as LYs and QALYs are obtained from PFS and OS values that were adjusted for HRs. In addition, PFS utility in the comparator arm also calculated as a weighted proportion of best supportive care to cabazitaxel. The results reflect a complex relationship between costs and utilities in the comparator arm and should be interpreted with caution. It is even more so in the context of a hybrid model, which further complicates the algorithm by applying a coefficient of 0.279 to the comparator PFS and OS to approximate the progression of non-responders.

As noted above, given 31% of patients enrolled in Re-SPECT failed to respond to treatment, it is possible that the nominated eligibility criteria (SUV_{max} >15 on PSMA PET at ≥1 site, and SUV_{max} >10 at all measurable sites), may not be sufficiently discriminatory for identifying a population who are likely to respond.

Although the estimates of the ICER remain high, as discussed in the Commentary to the MSAC 1686.1 resubmission ADAR, the following information is to inform MSAC in determining the reasonableness of the requested fee for ^{177}Lu PSMA i&t. This information is from a Dutch study (Quist et al., 2023[9]) that investigated the costs of mCRPC treatment in Dutch hospitals for currently reimbursed radiopharmaceuticals with a demonstrated overall survival benefit. A cost model that calculated the direct medical per-patient costs of ^{177}Lu PSMA i&t was developed, following clinical trial regimens. The model used both the VISION regimen (6-weekly administrations) and the SPLASH regimen (four 8-weekly administrations). The cost (see Table 12) was calculated based on the following:

- In Holland, ^{177}Lu PSMA i&t is a pharmacy preparation.

- Reimbursement is restricted to the treatment of mCRPC in adult men that are PSMA positive in the absence of a more suitable therapeutical (as a last resort treatment).

- Radiopharmaceuticals are accompanied by additional treatment procedures (e.g. diagnostic scans and observation). Costs for observation were only included for patients who were not hospitalised.

- Radiopharmaceutical treatment is subsidised by the hospital budget.

- A Dutch healthcare payer's perspective, which includes all direct medical costs related to mCRPC treatment with radiopharmaceuticals were included. Only variable cost parameters were considered, and these consisted of medication, administration, clinic visits, imaging, hospital admission, and supportive care. No discount rate was used, and the time horizon was equal to the administration period of radiopharmaceuticals.

- Prior to ^{177}Lu PSMA i&t treatment, the presence of PSMA receptors on the tumour cells was established using Ga-PSMA-PET/CT scans.

- All costs were inflated to 2021 prices in euros using the CPI index of the Dutch Central Bureau of Statistics.

- Treatment costs incorporated medication costs, administration costs, and outpatient visit for every injection.

- For ^{177}Lu PSMA i&t, the list price reflects the cost price of hospital preparation (i.e. raw materials, devices, and labour).

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[9] Quist SW, Paulissen JHJ, Wyndaele DNJ, Nagarajah J, Frerisk RD (2023). Costs of radium-223 and the pharmacy preparation ^{177}Lu-PSMA-I&T for metastatic castration-resistant prostate cancer in Dutch hospitals. *Journal of Medical Economics*, 26:1. https://www.tandfonline.com/doi/full/10.1080/13696998.2023.2183618

Table 12 Comparison of prices for ^{177}Lu-PSMA i&t

| | ^{177}Lu PSMA i&t; per patient costs | | ADAR |
	VISION regimen	SPLASH Regimen	
Medication	€42,546	€31,008	$19,965.00*
Administration	€1,299	€1,1039	$9,075.00*
Hospital Admission	€327	€262	
Observation	€667	€534	
Supportive Care	€1,205	€1,237	
Monitoring	€510	€408	
Imaging	€1,357	€1,342	$1,400
Total Costs	**€47,546**	**€35,866**	**$30,440**
AUD $***	$76,847.27	$57,969.21	$30,440
Cost per preparation (dose) cycle	7.4 GBq	6.8 GBq	7.0-8.5 GBq**
Cost from Table 2 Quist et al., 2023	€8,846	€7,752	
Cost per dose in $AUD	$14,335	$12,562	$5,500

Source: Table 4 Quist et al., 2023; VISION regimen was five 6-weekly injections of 7.4 GBq; SPLASH regimen is four 8-weekly injections of 6.8 GBq..

*   The total costs included the proposed per dose cost, includes $5,500 for preparation of ^{177}Lu-PSMA-i&t plus $2,500 for administration, immediate aftercare, and 24-hour post-therapy SPECT/CT (source, Table 102 of ADAR 1686) and PSMA PET scan. Regimen as nominated in ADAR of 3.63 cycles.

**   It was reported in ADAR 1686 that the dose per cycle was set at 7.0-8.5 gigabecquerel (GBq).

***   XE Currency converter accessed 27 March 2023
https://www.xe.com/currencyconverter/convert/?Amount=35866&From=EUR&To=AUD and from USD to AUD

The costs of regimens (cost per patient) in the table above are not directly comparable as they are different regimens in terms of number of cycles. For this reason, the cost per dose (cycle) was presented for comparison, and it appears that the fee requested in the current (and previous) ADAR is markedly lower than that of the pharmacy preparation in the Dutch Study.

The wholesale acquisition cost for ^{177}Lu PSMA 617 are quoted as US$42,500 per dose[10] (AUD$63,168), capped at six doses administered 6 weeks apart, leading to a maximum cost per patient of 6 cycles=~US$255K, (AUD~$384K). Cost of administration and selection with PSMA PET/CT would also need to be added.

Addendum to the FFP DCAR

In response to the ESC request for additional modelling with respect to treatment cost based on two limit cases (minimum and maximum discontinuations). (see Section 16. Key issues from ESC to MSAC), the assessment group conducted further scenarios testing differing clinical rules for progression (Table 13).

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[10] https://www.thejournalofprecisionmedicine.com/fda-approves-novartis-radiologand-pluvicto-for-psma-positive-mcrpc-with-imaging-cdx/ [accessed 13 December 2023]

Table 13: Results from the MSAC 1686 original model with relevant updates- Addendum

Step		Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER ($/QALY)
A	Original model, as presented in the MSAC 1686 PSD. Please note that the costs and incremental costs reported in Table 10 of the MSAC 1686 PSD are incorrect for the estimate of the ICER per QALY. The correct costs for each treatment and incremental costs are shown below and are consistent with the costs and incremental costs reported in Table 10 of the MSAC 1686 PSD for the estimate of the ICER per LY.					
	[177]Lu PSMA i&t	$74,380	$28,799	1.118	0.353	$81,653
	Cabazitaxel/BSC	$45,581		0.765		
B	Original model (MSAC 1686): updated. Continue with weekly treatment costs ($1,333.33 ^{177}Lu PSMA i&t and $102.65 cabazitaxel [includes prednisolone]), applied to patients who remain in PFS on a weekly basis [incorrect application of costs, approach underestimates costs]. This result was reported in Table 10 of the FFP DCAR Executive Summary.					
	[177]Lu PSMA i&t	$75,711	$32,715	1.101	0.301	$108,743
	Cabazitaxel/BSC	$42,996		0.800		
C	Original model (MSAC 1686): As per B and cost of ^{177}Lu PSMA i&t and cabazitaxel) applied every 6 weeks ($8,000) and 3 weeks ($307.94, including prednisolone), respectively. All patients get one cycle, then only those in PFS get subsequent ^{177}Lu PSMA i&t. Best case and optimistic scenario [absolute maximum discontinuations].					
	[177]Lu PSMA i&t	$77,019	$34,005	1.101	0.301	$113,033
	Cabazitaxel/BSC	$43,014		0.800		
D	Original model (MSAC 1686): As per C and cost of ^{177}Lu PSMA i&t applied to all surviving patients (rather than those in PFS) for first two cycles, according to item descriptor **BASE CASE** [maximum discontinuations].					
	[177]Lu PSMA i&t	$77,113	$34,100	1.101	0.301	**$113,346**
	Cabazitaxel/BSC	$43,014		0.800		
E	Original model (MSAC 1686): As per C and cost of ^{177}Lu PSMA i&t applied to all surviving patients (rather than those in PFS) for four cycles, based on VISION [minimum discontinuations].					
	[177]Lu PSMA i&t	$79,557	$36,563	1.101	0.301	$121,535
	Cabazitaxel/BSC	$43,014		0.800		
F	Original model (MSAC 1686): As per C and cost ^{177}Lu PSMA i&t applied to all surviving patients (rather than those in PFS) for six cycles. Worst case scenario [absolute minimum discontinuations].					
	[177]Lu PSMA i&t	$82,750	$39,757	1.101	0.301	$132,083
	Cabazitaxel/BSC	$43,014		0.800		

Step C assumes all patients receive one cycle of ^{177}Lu PSMA i&t and all subsequent treatment is restricted to those who remain progression-free. This analysis is considered to be the 'best case scenario' in terms of estimating the ICER; and represents the absolute maximum in terms of the number of patients who discontinue. Although inconsistent with the proposed two-step item descriptors (see below), there is potential for patients to discontinue following a single cycle of ^{177}Lu PSMA i&t given progression is defined as "... a rise in PSA of >2 ng/mL confirmed by 2 tests a minimum 2 weeks apart and/or evidence of new soft tissue metastases on diagnostic CT as per RECIST criteria".

Step D assumes all surviving patients receive two cycles of ^{177}Lu PSMA i&t. This analysis is consistent with the two-step initial (two cycles) and continuing (up to four cycles) item descriptors proposed in the MSAC 1686.1 ADAR resubmission and assumed in the FFP DCAR and is thus considered to be the updated base case. Based on the proposed item descriptor, this represents the maximum in terms of the number of patients who discontinue.

Step E assumes all surviving patients receive four cycles of ^{177}Lu PSMA i&t. This analysis is consistent with the VISION trial where all patients received four cycles; "two additional cycles (up to six cycles in total) could be administered, at the discretion of the treating physician, in patients who had evidence of response". This represents the minimum in terms of the number of patients who discontinue.

Finally, Step F assumes that all surviving patients receive all six cycles of ^{177}Lu PSMA i&t. While possible, may not be probable and represents the absolute minimum in terms of the number of patients who discontinue (i.e., zero) for reasons other than death.

As noted, Steps D ($113,346/QALY) and E ($121,535/QALY) are considered to represent the likely maximum and minimum discontinuations from treatment, respectively. The variation in the ICER between the base case (Step D; maximum) and (Step E; minimum) is +7.2%.

Table 14 presents sensitivity analyses, varying several parameters in the model, for the updated base case.

Table 14 Sensitivity analyses on the updated base case (Step D above) and cost of ^{177}Lu PSMA i&t applied to all surviving patients (rather than those in PFS) for first two cycles, according to item descriptor)- Addendum

		Incremental cost	Incremental QALYs	ICER	Impact
Base-case (Step D as above in)		**$34,100**	**0.301**	**$113,346**	-
Modelling assumptions					
A	Discount rate 0% for costs and outcomes	$35,130	0.341	$102,936	-9.2%
B	Discount rate 3.5% for costs and outcomes	$34,387	0.312	$110,216	-2.8%
C	Time horizon of 5 years	$33,430	0.267	$125,381	10.6%
Comparator					
D	Lower bound 95% CI ^{177}Lu PSMA i&t vs BSC OS HR (from 0.62 to 0.52)	$33,839	0.373	$90,807	**-19.9%**
E	Upper bound 95% CI for ^{177}Lu PSMA i&t vs BSC OS HR (from 0.62 to 0.74)	$34,449	0.220	$156,727	**38.3%**
F	Assume 100% BSC	$34,936	0.354	$98,586	-13.0%
G	Historic price of cabazitaxel (February 2022) Weighted public:private price of $1,068.78	$33,625	0.301	$111,770	-1.4%
Utilities					
H	15D utility values from Torvinen et al. (2013) (PFS: 0.80, PD: 0.67)	$34,100	0.321	$106,364	-6.2%
I	PFS: 0.86 (Krahn et al., 2007), PD: 0.635 (Wu et al., 2007) both sourced from Magnus et al. (2019)	$34,100	0.345	$98,832	-12.8%
J	Utility cabazitaxel = 0.7 and BSC = 0.7 for PFS health state in the comparator arm (the Applicant's pre-MSAC response)	$34,100	0.314	$108,711	-4.1%
Costs					
K	Decrease terminal care costs ($41,569) by 20%	$34,387	0.301	$114,301	0.8%
L	Increase terminal care costs ($41,569) by 20%	$33,812	0.301	$112,391	-0.8%
M	In the intervention arm, 25% of progressed patients have subsequent treatment with cabazitaxel (as in the comparator group)	$34,253	0.301	$113,854	0.4%
N	In the intervention arm, 14.9% of progressed patients have subsequent treatment with cabazitaxel (consistent with VISION trial)	$34,032	0.301	$113,121	-0.2%
Multivariate analyses					
D+I	^{177}Lu PSMA i&t vs BSC OS HR = 0.52; PFS: 0.86; PD: 0.635 (Magnus et al 2019)	$33,839	0.422	$80,129	-29.3%

Bold refers to changes +/- 15% to base-case ICER

Abbreviations: BSC, best supportive care; CI, confidence interval; CT, computed tomography; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ^{177}Lu PSMA i&t, lutetium-177 prostate-specific membrane antigen imaging and therapy; OS, overall survival; PD, progressed disease; PFS, progression-free survival.

Overall, variations in most of the parameters (univariate analyses) lead to low to moderate impacts on the ICER (less than 15% change). If considering changes that lead to a greater than 15% change in the ICER represents high impact, the following parameters are of interest:

1. Assumed effectiveness in terms of the incremental benefit of ^{177}Lu PSMA i&t compared with BSC in terms of OS.

Sensitivity analyses conducted using the lower and upper 95% confidence interval ranges around the OS HR from VISION (^{177}Lu PSMA i&t vs BSC) had substantial impacts on the ICER (decreased by 19.9% and increased by 38.3%, respectively). It is clear that the comparative effectiveness of ^{177}Lu PSMA i&t vs BSC (and vs cabazitaxel) would need to be greater than that accepted by the point estimates observed in the VISION (and TheraP) trials in order for the ICER to decrease meaningfully.

A multivariate analysis was conducted to combine the variations in the assumptions about the HRs used in the model. Setting OS HR ^{177}Lu PSMA i&t vs BSC at 0.52 (lower bound of the 95% CI from VISION) and with utility values from Magnus (2019)[11] applied, the reduction would be 29.3%, bringing the ICER to $80,129 (Analyses D+I). Uncertainty pertaining to utilities is discussed below.

2. Utilities

In the base case, EQ-5D utilities reported in Torvinen (2013)[12] were used. The utility estimates in Torvinen (2013) were elicited from a relatively small sample size (n=17 palliative patients; informing a PD utility of 0.59 (95% CI: 0.48, 0.70) and n=85 metastatic patients; informing a PFS utility of 0.74 (95% CI: 0.69, 0.80). These utilities have been applied since the original MSAC 1686 ADAR, however they have been criticised for lacking applicability to the treatment arms in the model. The commentary to the MSAC 1686 ADAR noted that "Torvinen (2013) did not provide details on how patients were defined as being metastatic or palliative. As such, it is unclear whether these patients adequately correspond to progression-free and progressed patients in the model (p.183)". To be precise, criteria for progressing to "palliative" care was unlikely to correspond to the criteria for disease progression used in the TheraP or VISION trials that informed the model. Nevertheless, the base case MSAC 1686 utility values were consistent with those used in the Olaparib (March 2021 PBAC PSD) and Abiraterone submissions to the PBAC (November 2012 PSD).

Generally, MSAC indicated a preference for a health state specific utilities rather than treatment specific utilities. However, the PBS also previously accepted a separate utility decrement associated with chemotherapy, although the value of a decrement and details on how the potential double-counting was avoided are not readily available. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-07/erlotinib.

An extensive review of all published utilities in the commentary to the MSAC 1686.1 ADAR was provided and found that there was a non-linear relationship between the symptom scores (diarrhoea, fatigue, urinary, bowel and erectile dysfunction that differentiate ^{177}Lu PSMA from cabazitaxel) and the QoL results, indicating that adjusting the utility value by a fixed number may not be methodologically correct. We found some evidence of disutility (-0.04) associated with chemotherapy (Diels, 2015), but the decisive factor for accepting the treatment-specific utility was that it was previously used by another assessment group in PET/CT application (Song, 2022). However, to avoid double-counting, Song (2022) used a separate set of disutilities for urinary, bowel and erectile dysfunction and applied Torvinen's (2013) utility values only to the proportion of patients who did not experience any of these symptoms. The potential for double-counting was noted in the commentary to the MSAC 1686 ADAR, which stated that 41% of metastatic patients in Torvinen (2013) were reported as having chemotherapy during metastatic disease. As such, the utility values from Torvinen (2013)

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[11] Magnus, A., et al. 2019. A Systematic Review and Meta-Analysis of Prostate Cancer Utility Values of Patients and Partners Between 2007 and 2016. MDM Policy Pract, 4, 2381468319852332.

[12] Torvinen S., et al. 2013. Health-related quality of life in prostate cancer. Acta Oncol, 52, 1094-101.

informing the progression-free health state may incorporate, to some extent, cabazitaxel-related disutility (p.197).

The utility values tested in the sensitivity analyses are the same as in the original MSAC 1686 ADAR and in the MSAC 1686.1 ADAR resubmission. With the exception of utility for PFS of 0.86 (Krahn 2007)[13], the values fall within the 95% confidence intervals reported in Torvinen (2013). However, none of these utilities were adjusted for toxicity of cabazitaxel (or chemotherapy in general) since it was not possible to judge the degree of potential double-counting.

In its pre-MSAC 1686.1 response, the applicant acknowledged the difficulties and uncertainties associated with assigning utility values to health states in the model as EQ-5D utility values by progression status from VISION remain unpublished. The most recent publication of the VISION trial results (Fizazi, 2023)[14] reported an observed EQ-5D-5L utility values for BSC of 0.5, consistent with the 0.59 used in the model, but also the unrealistically high utility score of 0.9 for patients in ^{177}Lu PSMA 617 arm (median age 71 years). In comparison, the mean EQ-5D-5L utility score in general population of Australian males aged 65-74 years is 0.87 (SD = 0.16) (McCaffrey, 2016[15]). It is unlikely that the American males diagnosed with metastatic castration-resistant prostate cancer would have a higher quality of life than the average Australian male of the same age.

In its pre-MSAC 1686.1 response, the applicant argued that a scenario assuming a 0.04 decrement in the PFS health state for both BSC and cabazitaxel should be considered (Table 2, pre-MSAC 1686.1 response). This is also reproduced in with amended parameters of the model. The ICER was moderately sensitive to the variation in utility parameters presented in , with a maximum decrease by 12.8% under the assumption of PFS utility set at 0.86. There is a high degree of uncertainty associated with measuring the QoL in the mCRPC population.

14.   Financial/budgetary impacts

The use of health technology in practice presented in this FFP DCAR is based on some changes to the previous ADARs and is based on the financial impacts presented for MSAC 1686 and 1686.1. The specified changes are listed below.

The financial implications to the MBS and PBS/RPBS resulting from the proposed listing of PSMA PET/CT and ^{177}Lu PSMA i&t, presented in this FFP DCAR are summarised in Table 15.

The estimates are derived using the following assumptions:

• the estimated population with mCRPC has been updated as the ABS has provided updated data for deaths for 2020, 2021 and 2022 [ABS, 3303.0]. The population commences in 2024 but now goes through to 2029.

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[13] Krahn M., et al 2007. Responsiveness of disease-specific and generic utility instruments in prostate cancer patients. Qual Life Res, 16, 509-22.

[14] Fizazi K, Herrmann K, Krause BJ, Rahbar K, Chi KN, Morris MJ, Sartor O, Tagawa ST, Kendi AT, Vogelzang N, Calais J, Nagarajah J, Wei XX, Koshkin VS, Beauregard JM, Chang B, Ghouse R, DeSilvio M, Messmann RA, de Bono J. Health-related quality of life and pain outcomes with [177Lu]Lu-PSMA-617 plus standard of care versus standard of care in patients with metastatic castration-resistant prostate cancer (VISION): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2023 Jun;24(6):597-610.

[15] McCaffrey N, Kaambwa B, Currow DC, Ratcliffe J. Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. Health Qual Life Outcomes. 2016 Sep 20;14(1):133. doi: 10.1186/s12955-016-0537-0. PMID: 27644755; PMCID: PMC5028927.

- The average growth rate for mCRPC has been increased to 1.418% (from 1.3%) due to these new releases from the ABS.
- The proportion of patients otherwise treated with cabazitaxel is 25% from 75% as in the resubmission ADAR (MSAC 1686.1).
- Average number of ^{177}Lu PSMA i&t cycles is 3.63 cycles for the base case (from TheraP and was a reduction when compared to 4.7 in the original ADAR).
- A two-step approach is also presented as described in the proposed MBS item descriptor.
  - The first step is the financial implications of all eligible patients receiving two cycles.
  - The next step is the financial implications if all eligible patients who respond after two cycles (69% based on Emmett et al., 2023) are then eligible for an additional cycle.
  - The final step is the financial implications if, as reported by Emmett et al., 2023 a proportion of responders, also receive an additional cycle (4th cycle; 34% of responders). Although, individual patients may be eligible to receive up to six cycles, evidence from TheraP and Flegar 2023[16] are reporting average number of cycles around 3-4. Evidence to calculate additional cycles was not available.
- Uptake has been changed to be consistent with the Application form (for both MSAC 1686 and 1686.1) and from the available evidence that reports on the adoption of ^{177}Lu PSMA [Flegar 2023]. Using these two sources, the initial uptake is 25% (which is greater than the 11.5% originally modelled) and each year this grows by 20% until by 2029 60% of the eligible population receive the intervention. This is consistent with the Application form for this intervention which stated that it was anticipated that 60% of the population would be treated. The issue of 20% growth each year in uptake (as opposed to a lower 10-15%) is to reflect the available evidence which describes a fast take up of ^{177}Lu PSMA i&t in the mCRPC population (sensitivity analysis is presented for the 10, and 15% growth rate).
- The cost of cabazitaxel and its administration have been updated to reflect the current costs, of $241.15 DPMA public and $286.58 DPMA private (weighted average $271.54).
- A post ^{177}Lu PSMA i&t use of cabazitaxel of 18%.
- As ^{177}Lu PSMA i&t is given in an outpatient setting (this is not necessarily the case in other countries) the maximum permissible gap of $98.70 applies.
- PBS co-payment for general patients is $30.00.

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[16] Flegar L, Thoduka SG, Librizzi D, Luster M, Zacharis A, Heers H, Eisenmenger N, Ahmadzadehfar H, Eiber M, Weber W, Groeben C, Huber J. Adoption of Lutetium-177 PSMA radioligand therapy for metastatic castration resistant prostate cancer: a total population analysis in Germany from 2016 to 2020. *Eur J Nucl Med Mol Imaging*. 2023 Jun;50(7):2188-2195. doi: 10.1007/s00259-023-06139-x. Epub 2023 Feb 24. PMID: 36826478; PMCID: PMC10199877.

Table 15 Net cost to the MBS and R/PBS (Base Case = 3.63 cycles)

Year	2024	2025	2026	2027	2028	2029
Eligible Population	3,126	3,170	3,215	3,261	3,307	3,354
Uptake rate	25.0%	30.0%	36.0%	43.2%	51.8%	62.2%
Number of MBS Services (PSMA PET)	781	951	1157	1409	1714	2086
Net MBS costs (PSMA PET)	$1,001,922	$1,219,354	$1,483,972	$1,806,016	$2,197,949	$2,674,938
Number of patients treated with ^{177}Lu PSMA i&t	704	856	1042	1268	1543	1878
Net MBS costs (^{177}Lu PSMA i&t)	$20,180,002	$24,559,368	$29,889,123	$36,375,516	$44,269,554	$53,876,718
Total net cost of PSMA PET and ^{177}Lu PSMA i&t	$21,181,923	$25,778,722	$31,373,095	$38,181,532	$46,467,503	$56,551,656
Savings to the MBS and PBS/RPBS from avoided cabazitaxel treatment						
Net cabazitaxel administration cost to MBS	-$129,824	-$157,998	-$192,286	-$234,015	-$284,800	-$346,606
Net cabazitaxel cost to PBS/RPBS	-$333,681	-$406,094	-$494,223	-$601,477	-$732,007	-$890,863
Net cost to the MBS and RPBS (cost of proposed listing minus savings from cabazitaxel services avoided)						
MBS	$21,052,099	$25,620,724	$31,180,809	$37,947,517	$46,182,703	$56,205,050
PBS/RPBS	-$333,681	-$406,094	-$494,223	-$601,477	-$732,007	-$890,863
Government (MBS + PBS/RPBS)	$20,718,418	$25,214,629	$30,686,586	$37,346,040	$45,450,697	$55,314,187
18% of post ^{177}Lu PSMA i&t receive cabazitaxel	$21,052,142	$25,620,776	$31,180,872	$37,947,594	$46,182,797	$56,205,165
***Two-step Approach ***						
All eligible patients receive initial 2 cycles	$11,990,598	$14,592,740	$17,759,586	$21,613,685	$26,304,182	$32,012,589
69% of eligible patients who respond after 2 cycles get 3rd cycle	$15,874,383	$19,319,364	$23,511,959	$28,614,411	$34,824,172	$42,381,545
34% of eligible patients who respond after 2 cycles get 4th cycle	$17,788,131	$21,648,426	$26,346,462	$32,064,044	$39,022,427	$47,490,885

Source: Attachment 2 'Mortality method' sheet
Abbreviations: Lu, Lutetium; MBS, Medicare Benefits Scheme; PSMA, prostate specific membrane antigen; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme
*Net Costs to the MBS and RPBS is based on the assumption that 18% of post Lu-PSMA patients receive cabazitaxel.

Compared to the original ADAR (MSAC 1686), the savings to the PBS/RPBS is reduced due to the co-payment reduction from $42.50 to $30 and also the significant decrease in the weighted public/private cost of cabazitaxel from $1,165.94 per cycle to $271.56 per cycle.

The base case of 3.63 cycles, based on TheraP, of ^{177}Lu PSMA i&t was chosen due to the articles by Emmett et al., 2023 and Flegar et al., 2023 reporting an average of three cycles per patient in their cohorts.

Increased costs to the MBS are incurred as the ADARs assumed patient co-payment of 15% for the PET/CT and ^{177}Lu PSMA i&t, whereas this assessment assumed that the maximum permissible gap of $98.70 would apply as this is an out-patient procedure.

The financial implications of this assessment are considerably higher than for the ADARs due to assumptions of higher initial uptake of ^{177}Lu PSMA i&t and higher growth in uptake over the six years (11.5% vs 20%). These assumptions are considered reasonable based on the information in the application form for MSAC 1686 & 1686.1 that quoted an initial uptake of approximately 25% of the reported eligible population and an aim that ^{177}Lu PSMA i&t would be available to 60% of the eligible population. Evidence presented from use of ^{177}Lu PSMA i&t in Germany supports a rapid uptake in the eligible population. The initial uptake of 25% is also consistent with the assumption that 25% of the comparator arm would be given cabazitaxel, a drug noted for its toxicity.

A limitation to the uptake of this technology will be the number of nuclear imaging departments able to offer this service currently and in the future. Unfortunately, this information was not available to inform this assessment.

15. Other relevant information

Nil.

16. Key issues from ESC to MSAC

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Main issues for MSAC consideration

Economic issues:

- Despite addressing many of the issues identified by previous MSAC, the fit for purpose (FFP) DCAR hybrid model generated new uncertainty. The hybrid model demonstrated the limitations of the data and evidence, and applying new methods that use these existing data requires assumptions and/or involves input transformations that are inherently uncertain.

- Despite remaining uncertainty around the ICER it is unlikely to fall below $100,000/QALY. This could potentially be estimated with respect to treatment cost based on two limit cases (minimum and maximum discontinuations). ESC advised that this additional remodelling should be done and provided before MSAC's consideration. Subsequently, the assessment group produced an Addendum (see above Section 13. Economic Evaluation) which included scenario testing using differing clinical rules for progression to model minimum and maximum treatment discontinuation.

- Whether it may be more appropriate to have a simplified item descriptor for therapy whereby continuation is based only on lack of disease progression rather than the number of cycles. However, uncertainty remains regarding how treatment response would be detected and treatment decision-making in practice. Specifically, there is uncertainty whether SPECT/CT would be performed after each cycle for the purposes of both disease progression monitoring and clinical decision-making, and how the decision would be made to terminate treatment in non-responders, and its implications to the economic evaluation.

Financial issues:

- The previously noted issues regarding key assumptions (initial uptake rate, growth of uptake rate, rate of cabazitaxel use) have been addressed.

- The financial impacts appear more plausible than in previous submissions but are still uncertain.

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ESC discussion

ESC noted that this resubmission requested Medicare Benefits Schedule (MBS) funding for a prostate-specific membrane antigen– (PMSA-) based treatment and diagnostic technologies. The treatment component consists of:

1. ^{177}Lutetium (^{177}Lu) PSMA imaging and therapy (^{177}Lu PSMA i&t) for treatment of progressive metastatic castrate resistant prostate cancer (mCRPC).

Eligibility for this treatment is determined by the following diagnostic test:

2. Whole-body PSMA positron emission tomography [PET]/computerised tomography [CT].

ESC noted that this codependent resubmission had been previously considered by MSAC at its July 2022 and July 2023 meetings. At its most recent consideration, MSAC accepted the previous evidence that ^{177}Lu PSMA i&t is acceptably safe and effective but continued to have concerns that the incremental cost-effectiveness ratio (ICER) was too high and uncertain. MSAC had also noted that the newly proposed two-step approach to treatment (up to a maximum of 2 cycles initially, then if disease progression had not occurred, up to a maximum of another 4 cycles) was not captured by the structure of the model and had considered that the financial impact was underestimated. MSAC therefore 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. MSAC also requested a revision to the model to reduce the uncertainty created by the patient-level data from different trials in the same model for determination of progression-free survival (PFS) benefits and costs associated with the intervention. MSAC also requested better justification (or removal) of the selected treatment-specific utility weights. Finally, although MSAC had preferred a more conservative time horizon of 5 years, it had considered a 7.5-year time horizon would likely be acceptable (1686.1 public summary document [PSD]).

ESC noted in consultation with the applicant, a fit-for-purpose (FFP) department-contracted assessment report (DCAR) was commissioned to progress the MSAC deferral and requested revisions to the economic model. ESC considered the revised economic model, its outcomes and updated financial analyses at this current meeting.

ESC noted the clinical evidence previously presented and considered there were no new clinical issues not previously considered.

ESC noted and welcomed consultation input from 12 professional organisations and 3 consumer organisations. ESC noted the strong support for this application from consumers and consumer organisations.

ESC noted consultation feedback from consumer groups that treatment with ^{177}Lu PSMA i&t has noticeable advantages over other treatments such as chemotherapy and radiation therapy, improving survival and quality of life for patients with mCRPC. Furthermore, it is a safe and efficacious treatment that has significantly less costs for both the government and patients than other treatments.

ESC noted that the economic evaluation used a hybrid model that apportioned progression free survival (PFS) and overall survival (OS) data from the VISION trial to reflect the proportion of responders in the Re-SPECT trial. As in the previous resubmission model, outcomes for the comparator treatment (a weighted comparator of 25% cabazitaxel and 75% best supportive care) were modelled using a proportional hazards approach, which applied hazard ratios for PFS and OS from the TheraP and VISION trials to the modelled PFS and OS for ^{177}Lu PSMA i&t.

ESC noted that the patient pathway also remained the same as the previous resubmission. Only patients who had not developed disease progression after receiving ^{177}Lu PSMA i&t in the first 2 cycles (responders) would be eligible to continue the treatment for up to 6 cycles. ESC noted

that non-responders (patients who developed disease progression in the first 2 cycles) would go on to have subsequent alternative treatment, but ESC considered it unclear how subsequent treatment was captured in the model. ESC noted from the model input summary that 18% of patients were assumed to receive subsequent cabazitaxel treatment. However, 31% of patients enrolled in the Re-SPECT trial were non-responders, and ESC considered that some responders would also progress to subsequent alternative treatment. ESC also queried if, in Australian clinical practice, SPECT/CT assessment would be performed after each cycle for the purposes of both disease progression monitoring and clinical decision-making, and how the decision would be made to terminate treatment in non-responders.

ESC noted that the FFP DCAR model appropriately explored two time-horizons: 7.5 years in the base case and 5 years in a sensitivity analysis. ESC also noted that the time on treatment was updated in the model, now estimated to be 8.88 weeks (or 1.48 cycles) for non-responders and 20.53 weeks (or 3.42 cycles) for responders. Costs were also updated to be current as at November 2023.

ESC considered the model inputs and extrapolation methods to be acceptable however, there remained several uncertainties with the FFP DCAR hybrid model. ESC questioned the feasibility of the modelling with respect to the available evidence, specifically regarding the treatment strategies (i.e. [177]Lu PSMA i&t treatment for up to 6 cycles, switching to an alternative treatment at week 6 if disease progression is detected to the current practice of best supportive care and treatment with cabazitaxel) and the costs based on response (from the Re-SPECT trial) versus PFS/OS outcomes (from the VISION trial). ESC also noted that the limitations of the available evidence translated into input data issues; specifically, a lack of subgroup Kaplan–Meier (KM) curves, time-to-event data, head-to-head data, and a single source for the required parameters. ESC also noted that both a state-transition model (STM) and partition-survival model (PSM) were used. ESC considered that this introduced conceptual issues due to the use of two distinct modelling paradigms ('probability of' and 'proportion affected').

In addition, ESC noted that the FFP DCAR's hybrid model assumed that the progression of non-responders could be modelled using the comparator arm. The assessment group stated this was done because all patients were assumed to be identical at baseline in both arms. However, ESC considered that non-responders were likely to be different in each arm, and that it may not be reasonable to assume they would progress in the same way. However, ESC considered it was unclear which direction this would impact the ICER because of the conceptual issues associated with the hybrid model.

ESC noted that the FFP DCAR hybrid model resulted in a base case incremental cost of $31,946, a quality-adjusted life year (QALY) gain of 0.208 and an ICER of $153,583/QALY. However, ESC agreed with the assessment group and considered the relationship between PFS, progressed disease (PD) and OS, and responder and non-responder status, suggested the integrity of the model was compromised. ESC noted the hybrid model did not quantify the higher level of uncertainty as a numerical range for alternative interpretations. Therefore, ESC considered these ICER estimates to be unreliable as a basis for decision making.

ESC noted that the assessment group considered the most reliable ICER estimate was informed by an alternative base case model which was revised based on the original PSM model. This was because it relied on VISION trial data for PFS and OS, did not use patient-level data from other studies for PFS benefits and costs, and based time on treatment only on progression (and not on number of cycles). This model resulted in an ICER of $108,742/QALY. However, ESC noted that this model does not explicitly capture response to treatment, instead using PFS as a proxy (as per standard PSM modelling approaches). ESC queried whether this may potentially underestimate the ICER by representing an optimised treatment cost.

ESC considered that, based on a comparison across several presented models, it appeared that the ICER was unlikely to fall below $100,000/QALY. However, it was unclear whether $108,742 and $153,583 indicated a plausible range. It was also not clear where the true ICER would fit within that range, or if it would be within that range at all. ESC noted the driver across these ICER ranges were the differences in assumptions regarding ^{177}Lu PSMA i&t treatment discontinuation and the approach to treatment cost calculation (see Table 10). ESC queried whether the ICER range could be estimated with respect to treatment cost based on two limit cases (minimum and maximum discontinuations). ESC advised that this additional remodelling should be done and provided before MSAC's consideration (see below in box).

ESC considered the sensitivity analyses performed on the FFP DCAR model were not informative for decision making in light of more fundamental problems with the base-case and did not help with the quantification of the key uncertainty of this model. In particular, ESC considered the analysis assuming a comparator of 75% cabazitaxel and 25% best supportive care was arbitrary and uninformative.

Note: to further clarify ESC advice to MSAC regarding additional modelling, discussions were held with the assessment group following the ESC meeting. The assessment group produced an Addendum (see above Section 13. Economic Evaluation) which included the results of the original model presented in the MSAC 1686 PSD, with a series of various adjustments made to update the time horizon, estimates of effect, comparator split, utilities, unit costs and application of costs from a weekly basis to application of costs at the time of treatment; and additionally reports scenarios testing differing clinical rules for progression to address ESC request to estimate what the ICER range could be with respect to treatment cost based on two limit cases [minimum and maximum discontinuations]. This resulted in an updated base case of $113,346 per QALY which was consistent with the two-step initial (two cycles) and continuing (up to four cycles) item descriptors proposed in the MSAC 1686.1 ADAR resubmission and thus considered to be the updated base case. As noted in the Addendum, Step D ($113,346/QALY) and E ($121,535/QALY) are considered to represent the likely maximum and minimum discontinuations from treatment, respectively. Sensitivity analyses on the updated base model showed moderate impacts of the assumed health state utility values (the ICER ranging from $98,832 to $108,711/QALY over the values tested), and highlighted the incremental OS benefit as a key driver of the model the ICER ranged from $90,807 to $156,727/QALY for the lower and upper bound 95% CI for OS HR in ^{177}Lu PSMA i&t vs best supportive care, respectively).

Overall, ESC considered that the FFP DCAR model partly addressed MSAC's concerns around the use of patient-level data, treatment-agnostic health state utility, and time-horizon but did not reduce uncertainty. Furthermore, ESC considered that the model introduced a new type of uncertainty: the hybrid model is not methodologically robust because it combines two distinct modelling paradigms and uses data that are not sufficiently comprehensive, resulting in the model's elements not being mathematically precise. Additionally, ESC noted that the assessment group made efforts to capture the two-step treatment approach accurately while recognising that the extent to which clinical decision-making will align with the model and the proposed MBS items for therapy (up to 2 in the initial treatment phase item and up to 4-cycles in the continuing treatment phase treatment item) in practice remained unclear.

ESC considered that the availability of new data was unlikely to provide enough detail to fully address uncertainties, and that opportunities for the original investigation had been largely exhausted due to the limitations of the data and methods.

In addition, ESC queried whether it may be more appropriate to have a simplified item descriptor whereby continuation is based only on disease progression, rather than the number of cycles. However, uncertainty also remains regarding how response is detected and treatment decision-

making in practice. Specifically, there is uncertainty whether SPECT/CT would be performed after each cycle for the purposes of both disease progression monitoring and clinical decision-making, and how the decision would be made to terminate treatment in non-responders, and its implications to the economic evaluation.

ESC noted that the FFP DCAR provided additional information to inform MSAC in determining the justification of the requested fee for ^{177}Lu PSMA i&t (see Table 12). This was based on a Dutch healthcare payer's perspective, with all costs inflated to 2021 prices in euros using the consumer price index of the Dutch Central Bureau of Statistics and did not include fixed or capital costs. ESC noted these costs were not applicable to the Australian setting.

ESC noted the approach used to estimate the financial impact. The estimated population with mCRPC was updated to reflect the 2024–29 period, and the average growth rate increased from 1.3% to 1.418% (based on new data from the Australian Bureau of Statistics). The comparator split (25% cabazitaxel and 75% best supportive care) was the same as that used in the previous submission. The average number of ^{177}Lu PSMA i&t cycles in the base case decreased from 4.7 in the original application to 3.63 (based on the TheraP trial). Cabazitaxel and administration costs were also updated.

Regarding the stepwise approach to treatment, it was assumed that:

- All eligible patients receive 2 initial cycles.
- All eligible patients who respond after 2 cycles (69% based on Emmett 2023) receive an additional cycle; 34% of responders receive a fourth cycle (Emmett 2023). Although individual patients may be eligible to receive up to 6 cycles, evidence (TheraP, Flegar 2023) shows that patients receive an average of between 3 and 4 cycles.
- The initial uptake is 25%, growing by 20% each year until reaching 60% of the eligible population in 2029. The initial uptake increased from 11.5% in the original application. ESC considered that the higher uptake rate was more appropriate based on the toxicity of cabazitaxel however, uptake may be limited by availability. ESC noted that the higher uptake rate was supported by evidence from Germany.
- Growth rate values are 10% and 15% (sensitivity tested).
- Cabazitaxel use after ^{177}Lu PSMA i&t is 18%.

ESC noted that the overall financial impact was estimated to be $21.1 million in Year 1 increasing to $56.2 million in Year 6. ESC considered these figures to be more plausible than in previous applications, but still uncertain.

ESC also noted that, as previously identified by MSAC (1686.1 PSD), patent-related matters identified during the consultation feedback process would require consideration by government before the listing of any MBS items resulting from this application (if supported).

17. Applicant comments on MSAC's Public Summary Document

The applicant advises that a review of the item descriptors would be beneficial to ensure the MBS items are fit for purpose.

18. Further information on MSAC

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