

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1686.1 – ¹⁷⁷Lutetium 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: 27 July 2023

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

A codependent re-application (application 1686.1) was received by the Department of Health from a group of academic specialists, co-sponsored by the Australasian Association of Nuclear Medicine Specialists (AANMS), requesting, in the context of progressive metastatic castrate-resistant prostate cancer (mCRPC), Medicare Benefits Schedule (MBS) listing of:

- (i) prostate specific membrane antigen positron emission tomography/computerised tomography (PSMA PET/CT) to determine eligibility for
- (ii) ¹⁷⁷Lutetium prostate-specific membrane antigen (¹⁷⁷Lu-PSMA) and 24-hour post-therapy single-photon emission/computed tomography/computerised tomography (SPECT/CT).

As discussed below, MSAC has referred to specific ¹⁷⁷LuPSMA products, either as ¹⁷⁷Lu PSMA imaging scan and therapy (¹⁷⁷Lu PSMA i&t) or ¹⁷⁷Lu PSMA-617.

2. MSAC's advice to the Minister

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

MSAC noted the high clinical need for this population with advanced disease. MSAC reconsidered the evidence base and the additional perspectives comparing ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 products. MSAC noted the limitations in the evidence base but concluded that the two products are mutually noninferior and thus considered the evidence for ¹⁷⁷Lu PSMA-617 to be relevant for ¹⁷⁷Lu PSMA i&t. Thus, MSAC accepted the evidence that ¹⁷⁷Lu 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 noted that the proposed two-step approach to treatment was not captured by the structure of the model. MSAC also considered that the financial impact was underestimated.

MSAC deferred its advice and requested that a revised economic evaluation be conducted with the model structure corrected to capture the two-step approach to treatment proposed in the

MBS items and reduce the uncertainty created in the model by the patient-level data from different trials in the same model for determination of PFS benefits and costs associated with the intervention. In addition, MSAC requested better justification (or removal) of the selected treatment specific utility weights.

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

Consumer summary

This is the second application (resubmission) from a group of academic specialists, co-sponsored by the Australasian Association of Nuclear Medicine, requesting Medicare Benefits Schedule (MBS) listing of ¹⁷⁷Lutetium prostate-specific membrane antigen (¹⁷⁷Lu-PSMA) therapy to treat patients with metastatic castrate-resistant prostate cancer. Also requested is MBS listing of whole-body prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computerised tomography (CT), which will be used to determine treatment eligibility. This is the second time that MSAC has considered this application.

Metastatic castrate-resistant prostate cancer is a type of advanced prostate cancer that has spread to other parts of the body. 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 cancers cells are found to have high levels of PSMA, then 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 resistant prostate cancer that has not responded to standard treatments. This new therapy uses a radioactive chemical (also know 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. ¹⁷⁷Lu PSMA i&t is a type of PSMA-targeted radionuclide therapy.

A new two-step approach to ¹⁷⁷Lu PSMA i&t therapy (referred to as ¹⁷⁷Lu-PSMA in proposed MBS items) was proposed in this resubmission. In this approach, all patients who are eligible will receive an initial 2 cycles (doses) of ¹⁷⁷Lu 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, then they will be eligible to continue treatment for another 4 cycles. If the tests show no improvement despite ¹⁷⁷Lu PSMA i&t treatment, then it will be recommended that they stop ¹⁷⁷Lu PSMA i&t and try a different treatment instead.

MSAC acknowledged the clinical need for this therapy and that patients prefer it over other last-line options. MSAC also considered it to be a safe and effective therapy option for men with metastatic castrate-resistant prostate cancer for whom most of the other standard available therapies had not been effective. However, MSAC was concerned that the newly proposed two-step approach to treatment was not modelled correctly and as a result could not be sure whether the therapy represented good value for money. Also, given the known consumer preference for this therapy, MSAC considered the proposed utilisation to be underestimated.

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

MSAC deferred its advice on funding 1) ¹⁷⁷Lu 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 ¹⁷⁷Lu PSMA i&t therapy. MSAC considered ¹⁷⁷Lu PSMA i&t therapy to be a

Consumer summary

comparatively safe and effective treatment, but because of uncertainty in the economic model were unsure whether the therapy would represent good value for money. MSAC advised that it would reconsider this application following remodelling of the economic evaluation.

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

MSAC noted that this application from a group of academic specialists and co-sponsored by the AANMS, is for Medicare Benefits Schedule (MBS) funding of ¹⁷⁷Lu PSMA therapy to treat patients with progressive or symptomatic mCRPC in patients who have received at least one androgen receptor signalling inhibitor and at least one line of chemotherapy (docetaxel +/- cabazitaxel). The intervention would replace or displace cabazitaxel and displace best supportive care.

MSAC noted that this is a resubmission, with the previous submission considered by MSAC in July 2022.

MSAC recalled that, during its previous consideration of application 1686, it had acknowledged that there was a high clinical need for this population with advanced disease, and the consumer preference for ¹⁷⁷Lu PSMA therapy over its comparators of best supportive care and cabazitaxel. At that time, MSAC noted the limitations in the evidence comparing ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 products, but concluded from the evidence available that these two products are mutually noninferior and thus considered the evidence for ¹⁷⁷Lu PSMA-617 to be relevant for ¹⁷⁷Lu PSMA i&t. However, MSAC did not support the application because of uncertainties around the economic model, including the ICER was considered too high and uncertain – the ICER per quality-adjusted life year (QALY) was close to \$100,000 for several potentially plausible scenarios, which MSAC considered to be unacceptably high for the proposed population and estimated utilisation.

MSAC noted that this resubmission mainly focused on the economic evaluation of the intervention.

MSAC noted that there continues to be public interest and support for this application from all consumer organisations and most other organisations who provided consultation input. MSAC also noted and considered the consultation input from those who were not supportive of the application, including from commercial organisations who considered there is insufficient high-quality evidence to support the claim of equivalence between ¹⁷⁷Lu PSMA i&t and ¹⁷⁷LuPSMA-617, and therefore it is not valid to use studies on ¹⁷⁷Lu PSMA-617 to support claims of efficacy and safety for ¹⁷⁷Lu PSMA i&t.

MSAC further noted that patent-related issues arising from any manufacture, use or administration of ¹⁷⁷Lu PSMA i&t in Australia were again raised in the public consultation. MSAC noted the pre-MSAC response also provided advice upon these matters. MSAC noted that advising on patent matters is not within its Terms of Reference and considered that this uncertainty would require further consideration by government prior to the listing of any MBS items as a result of this application (if subsequently supported). MSAC's consideration proceeded on the basis of the current information before it and subject to the applicants having a legal right to use ¹⁷⁷LuPSMA i&t in Australia.

MSAC reconsidered the available evidence base and new information and submissions comparing ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 products. MSAC noted that ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 have related, but not identical, structures, with the differences being their chelators and linking portions. MSAC noted the pre-MSAC response, in which the applicant

referred to recent procedure guidelines from the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging (United States) that suggested that both ¹⁷⁷Lu PSMA products could be considered as equivalent¹. MSAC considered that there was no new substantive clinical trial data that changed MSAC's previous conclusion of mutual noninferiority between the two products – ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 have similar safety, efficacy, biodistribution and are radioequivalent, despite both products using different dosing schedules. Therefore, despite the limitations in the evidence comparing ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 products, MSAC accepted that these two products are mutually noninferior for patient outcomes. Therefore MSAC considered the evidence for ¹⁷⁷Lu PSMA-617 to be relevant for ¹⁷⁷Lu PSMA i&t, and therefore accepted the results of the clinical evaluation and the clinical aspects of the modelled economic evaluation across these two ¹⁷⁷Lu PSMA products. Thus, MSAC also accepted the evidence that ¹⁷⁷Lu PSMA i&t therapy is acceptably safe and effective. However, MSAC recalled it was not prepared to generalise this conclusion to include other ¹⁷⁷Lu PSMA products and instead MSAC considered it necessary for an MBS item descriptor to appropriately define the ¹⁷⁷Lu PSMA therapy (if subsequently supported). Throughout this document, MSAC has therefore referred to specific ¹⁷⁷Lu PSMA products, either ¹⁷⁷Lu PSMA i&t or ¹⁷⁷Lu PSMA-617.

MSAC noted that there were three items proposed for this service: one for PSMA PET/CT and two for ¹⁷⁷Lu PSMA i&t treatment (referred to as ¹⁷⁷Lu-PSMA in proposed MBS items for therapy; see MBS item ZZZZ [initial treatment] in Table 3 and MBS item YYYYY [continuing treatment] in Table 4). MSAC noted that the descriptor for PSMA PET/CT included the changes previously suggested by MSAC, but otherwise remained unchanged from what was presented in the previous application. Conversely, unlike the previous application, ¹⁷⁷Lu PSMA i&t treatment was separated into two items that covered initial (up to a maximum of 2 cycles) and continuing (up to a maximum of 4 cycles) treatment, with single-photon emission CT (SPECT) performed 24 hours post-infusion for each cycle. Eligibility for the continuing treatment item was only for those patients whose disease had not progressed following the initial two cycles of ¹⁷⁷Lu PSMA i&t treatment. It was proposed that absence of disease progression should be defined as no PSA rise or no new sites of soft tissue metastatic disease on CT. MSAC noted that this new two-step approach had implications for the economic model (discussed below).

MSAC noted that the proposal for the initial phase of ¹⁷⁷Lu PSMA i&t treatment to consist of two cycles was based on the results from Emmett et al. (2023)² (the Re-SPECT study). The study found that both serum prostate specific antigen (PSA) response and changes in tumour volume on a SPECT/CT scan can predict how patients will respond to treatment after the second dose (or after six weeks), and that adjusting treatment intervals based on early response biomarkers may improve patient outcomes. Results from the Re-SPECT study also informed the applicant's approach to provide continuing ¹⁷⁷Lu PSMA i&t treatment only to patients who did not demonstrate disease progression and ceasing ¹⁷⁷Lu PSMA i&t treatment in patients with early disease progression. MSAC noted ceasing ¹⁷⁷Lu PSMA i&t treatment in patients with early disease progression may give them the opportunity to access alternative, potentially more effective treatment. Overall, MSAC considered it appropriate to separate ¹⁷⁷Lu PSMA i&t treatment into initial (two cycles) and continuing (four cycles) treatment items.

¹ Kratochwil et al 2023 [Joint EANM/SNMMI procedure guideline for the use of ¹⁷⁷Lu-labeled PSMA-targeted radioligand-therapy \(¹⁷⁷Lu-PSMA-RLT\)](#). *Eur J Nucl Med Mol Imaging*. 2023 Jul;50(9):2830-2845.

² 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.

The Re-SPECT study also found that allowing men who showed good treatment response based on biomarker levels (35% of cohort) to have a treatment break or “treatment holiday” (for a median of six months), may improve quality of life in men who often have treatment fatigue and side effects. This approach may lead to lower costs associated with reduced utilisation of the intervention and thus possibly improved cost-effectiveness. MSAC considered that, while there should be an allowance for a “treatment holiday” for those patients who respond early and well to treatment, it did not need to be specified in the item descriptor and should be left to clinical judgement. MSAC noted that the pre-MSAC response agreed as a treatment holiday could be incorporated in the treatment regimen if the patient does not progress during the holiday and the treating physician considers it clinically appropriate.

MSAC further considered the assessment of disease response and progression. MSAC noted that the applicant agreed that a 50% or more reduction in PSA (based on the Re-SPECT study), as well as SPECT/CT 24 hours following each treatment, were the best ways to assess treatment response. Regarding the timing of response assessment, MSAC noted from the Re-SPECT study that progression may be determined as early as week six (or one day after the second dose is given), rather than at 12 weeks (or just before the third cycle). MSAC considered that the timing of the assessment did not need to be specified in the item descriptor. For the assessment of disease progression, MSAC noted the applicant proposed an amendment that the 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 noted that the Response Evaluation Criteria in PSMA-PET/CT (RECIP) 1.0 could be used to assess disease progression, however considered that any further tests needed to assess disease progression could be left to clinical judgement and did not need to be specified in the item descriptor.

MSAC recalled that the proposed fee of \$8,000 per dose would be sufficient to cover the costs of safe delivery of the service across all settings in Australia.

MSAC noted that the structure of the economic model, which was based on a cost-effectiveness and cost-utility analysis, was unchanged from the previous application. The model used a proportional hazards approach and partitioned survival model, with a cycle length of one week and using three health states. MSAC noted that the ICER in the resubmission was \$73,622, which was less than the ICER in the previous submission (\$81,653).

MSAC considered that the new 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. For example, the model allowed patients to exit treatment weekly (after each model cycle); however, MSAC considered this to be clinically unrealistic as it was more likely that a group of patients would stop treatment after two cycles (once they were determined to be non-responders). MSAC considered this may lower the ICER as a greater proportion of non-responders would leave the model after the first or second cycle. 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 also noted that the model used Time on Treatment (ToT) to calculate the cost of ¹⁷⁷Lu PSMA i&t treatment cycles. This resulted in the unit cost for ¹⁷⁷Lu PSMA i&t treatment only applying to progression-free patients, with the implicit assumption that only progression-free patients remain eligible for treatment on a week-by-week basis. MSAC noted that, in the original model, ToT was equal to progression-free survival (PFS) extracted from the graphical representation of the Kaplan–Meier survival data from the VISION trial. In the revised model, ToT was decoupled from PFS and, for the first 36 weeks (the maximum duration of the six cycles of

treatment), was based on the Kaplan–Meier survival data from the TheraP trial. Apart from the ToT values used in cost calculation, the rest of the model (that is, PFS, OS [overall survival], LYs [life years] and QALYs) remained linked to Kaplan–Meier data from the VISION trial for the entire span of the model, starting from week one. MSAC considered this to violate the model’s integrity, as it introduced inconsistencies in the model treatment of costs and gains. MSAC noted that using this approach for the economic model reduced the total cost of treatment by 21%, as TheraP had a higher rate of progression than the VISION trial and, therefore, a lower rate of patients remaining on treatment. MSAC noted that there was no adjustment in the cost calculation that would correspond to the initial treatment phase item descriptor, which for the first two cycles (12 weeks of treatment) the ¹⁷⁷Lu PSMA i&t unit cost would apply to all surviving patients, whether remaining progression-free or not. When this was corrected for during evaluation using the VISION trial survival data to determine ToT in one-way sensitivity analyses, the ICER increased by 29%, to \$94,936. MSAC considered these plausible estimates to be the key source of uncertainty as to whether ¹⁷⁷Lu PSMA i&t therapy would be acceptably cost-effective.

Regarding treatment-dependent utilities, MSAC noted that the utility in the PFS state was a weighted average of cabazitaxel and best supportive care. In the original model, treatment-agnostic utility values were used for the health states (PFS = 0.74; progressed disease [PD] = 0.59; death = 0), but the revised model used treatment-specific utilities (¹⁷⁷Lu PSMA i&t = 0.74; cabazitaxel/ best supportive care = 0.62; weighted cabazitaxel+ best supportive care utility of PD = 0.59). MSAC considered that treatment-specific utilities may not be reasonable, as there is a complex non-linear relationship between the type of treatment, the stage of disease progression, symptoms (including adverse events) and quality of life (QoL). MSAC also noted that best supportive care was given the same utility in the PFS state as in the PD state (0.59), which it did not consider reasonable. MSAC noted that this created a QoL increment that favoured the intervention; using a utility of 0.74 for best supportive care in the PFS state increased the ICER by 16%. MSAC noted that, apart from the disutility of 0.04 that applied to cabazitaxel patients (to reflect its toxicity), there was no other treatment-specific utility estimate in the proposed population that could be used in the PFS health state with any degree of certainty. MSAC noted the pre-MSAC response, which the applicant acknowledged the uncertainties with the selected utility values and provided additional one-way sensitivity and scenario analyses which attempted to address the ESC’s concerns (see Table 10). MSAC noted that this resulted in a moderate impact on the base case ICER (increase of 10-16%).

MSAC considered the time horizon used in the economic model. The original model used a time horizon of 10 years. In its previous consideration, MSAC noted that a 10-year time horizon was inconsistent with previous advice from the Pharmaceutical Benefits Advisory Committee (PBAC) for medicines in later-line mCRPC treatment, and advised that a time horizon of 5 years would be more appropriate in the base case model (noting that this would increase the ICER). However, the current model used a time horizon of 7.5 years. MSAC noted that the applicant considered that a 7.5-year time horizon was appropriate, given the “plateau” for ¹⁷⁷Lu PSMA-617 in OS reported in several trials, including the more mature data for TheraP compared to PROfound (Olaparib) where a 7.5-year time horizon was claimed to be accepted by the PBAC. However, MSAC noted that the available data were for 3 years of follow-up, with the remainder of the analysis relying on extrapolation. MSAC also considered that the interpretation of the observed plateau in the Kaplan Meier curve was limited by the low remaining numbers at risk at 3 years in the TheraP trial. However, MSAC noted that reducing the horizon to 5 years had a low-moderate impact on the base case ICER (increase of 8%). Although MSAC had a preference for a more conservative time horizon of 5 years, MSAC considered a 7.5 year time horizon would be likely to be acceptable.

MSAC noted that the model did not include incremental costs of extra tests used to define clinical progression. MSAC considered this to be appropriate as these tests were likely to be clinically driven in response to patients' symptoms irrespective of being on treatment with ¹⁷⁷Lu PSMA i&t or cabazitaxel or best supportive care. MSAC also noted that the inclusion of these costs only made a small difference to the ICER (increase of 5%).

MSAC considered the financial estimates to likely be underestimated, based on an uptake of 11.5% likely being too low. Justification for why the uptake rate for this last-line therapy would remain under 20% for the eligible population after five years was not provided. MSAC noted that the use of the health technology in practice that was presented in the resubmission was based on some changes to the previous submission, and not a new presentation of the financial impacts, including disaggregation of utilisation estimates for the proposed 2-stage approach to treatment. MSAC also noted that the commentary appropriately included the financial implications of the use of cabazitaxel following ¹⁷⁷Lu PSMA i&t treatment.

Overall, MSAC deferred its advice to the Minister in relation to the funding of ¹⁷⁷Lu PSMA i&t therapy and PSMA PET/CT for the treatment of progressive or symptomatic mCRPC. MSAC acknowledged that there was a high clinical need, consumer preference for ¹⁷⁷Lu PSMA therapy over cabazitaxel or best supportive care, and that equity of current treatments was an issue. MSAC also acknowledged that direct evidence comparing ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 was not available and would be unlikely to eventuate, but concluded on consideration of the evidence before it, that MSAC's previous conclusion of mutual noninferiority remained sound. Thus, MSAC accepted that ¹⁷⁷Lu PSMA i&t therapy is acceptably safe and effective. MSAC considered that the new two-step approach to treatment whereby treatment is split into initial (up to a maximum of 2 cycles) and continuing treatment (up to a maximum of 4 cycles) was appropriate but that the applicant's economic model did not appropriately capture this, including the problematic use of different trial data for the determination of the PFS benefits and costs associated with the intervention. When this was corrected for in the commentary the ICER per QALY was close to \$100,000 which MSAC considered to be unacceptably high for the proposed population and expected utilisation. Thus, MSAC continued to have concerns that the ICER was too high and uncertain. MSAC noted consistent with the previous submission, the cost effectiveness was more favourable when placed after cabazitaxel and against best supportive care; however MSAC considered the proposed place in therapy appropriate because many (but not all) men forgo cabazitaxel treatment (due to its toxicity) in favour of palliative treatment (i.e. best supportive care). In addition, MSAC also considered that the financial impact was underestimated due to a likely higher uptake rate than assumed for a comparatively safe and effective therapy used in last line.

MSAC requested that a revised economic evaluation be conducted:

- The model structure corrected to capture the two-step approach to treatment (based on the Re-SPECT study) proposed in the MBS items for ¹⁷⁷Lu 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.
- The treatment specific utility weights require better justification (or removal).

This would allow a more accurate estimate for the ICER including whether ¹⁷⁷Lu PSMA i&t therapy was acceptably cost effective at the proposed price of the therapy.

MSAC advised that the re-entry pathway would first involve consideration by the MSAC Executive, who will then advise whether the application should proceed to ESC or MSAC.

4. Background

Application 1686 was first considered by MSAC at the July 2022 meeting. MSAC acknowledged the high clinical need for this population with advanced disease, and the consumer preference for ¹⁷⁷Lu PSMA therapy over its comparators of best supportive care and cabazitaxel. MSAC noted the limitations in the evidence comparing ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 products, but concluded from the evidence available that these two products are mutually noninferior and thus considered the evidence for ¹⁷⁷Lu PSMA-617 to be relevant for ¹⁷⁷Lu PSMA i&t. MSAC accepted the high certainty from the evidence that ¹⁷⁷Lu PSMA i&t therapy is acceptably safe and effective, but that the incremental cost-effectiveness ratio (ICER) was too high and uncertain (1686 Final PSD p1-2).

This ADAR to MSAC addresses the key matters of concern as outlined in the public summary document (PSD) for Application 1686 and summarised in Table 1 below.

Table 1 Summary of key matters of concern

Component	Matter of concern	How the current assessment report addresses it
Comparator	MSAC considered a comparator weighting of 75% best supportive care and 25% cabazitaxel appropriate (PSD p6).	The base-case economic analysis has been updated to use this comparator weighting. <i>This has been reasonably adjusted in the modelled economic evaluation.</i>
MBS item	MSAC considered that the proposed item descriptor for ¹⁷⁷ Lu PSMA i&t did not specify how 'evidence of disease progression' should be measured for treatment with ¹⁷⁷ Lu PSMA i&t to cease before 6 cycles (i.e. prostate specific antigen (PSA) or radiographic progression as per TheraP or image-based progression only as per VISION). The definition of PFS had implications for the cost-effectiveness and overall cost of listing ¹⁷⁷ Lu PSMA i&t on the MBS. (PSD p10).	The proposed MBS items for ¹⁷⁷ Lu PSMA i&t (referred to as Lu-PSMA in proposed MBS items for therapy) has been updated to include separate MBS items for initial and continuing treatment phases and includes a definition of disease progression based on PSA and radiographic progression. <i>The continuing treatment item descriptor is insufficiently defined with respect to evidence of disease progression and how and when this should be measured.</i>
Cost-effectiveness	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 CEA has been updated taking into account feedback from MSAC, the updated restriction and further information on time on treatment, response to therapy and quality of life. <i>Methods used to adjust for time on treatment and utilities applied require consideration, see below.</i>
Financial impact	Updates to the financial impact based on the above issues.	The financial impact has been updated taking into account the updates to the comparator weighting and time on treatment. <i>The financial estimates however, do not consider treatment with cabazitaxel following ¹⁷⁷Lu PSMA i&t therapy.</i>

Abbreviations: 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: Compiled during evaluation from Table 1, p9 of the ADAR

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 ¹⁷⁷Lu PSMA i&t, is produced under Good Laboratory Practice (GLP) in Australia. GLP-compliant production of ¹⁷⁷Lu PSMA i&t is the current standard of care (SoC) for the provision of radiopharmaceutical treatments across Australia, within trials and in clinical practice. It is routinely used in nuclear medicine departments for radiopharmacy production across Australia. GLP production of ¹⁷⁷Lu 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 1686 PSD (with the suggested changes being accepted), as does the requested fee. As noted in the previous PSD, outpatient treatment is appropriate and currently in place with some providers, in these cases the greatest permissible gap (GPG; \$93.20) would apply.

Table 2 ADAR 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 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%* = \$1,206.80

Source: Table 2, p10 of the ADAR. This is consistent with the changes suggested to the item descriptor in Table 1, p8 of the MSAC 1686 public summary document (PSD)

* 85% benefit reflects the 1 November 2022 Greatest Permissible Gap (GPG) of \$93.20. All out-of-hospital Medicare services that have an MBS fee of \$621.50 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).

Note, the current ADAR, unlike the previous ADAR, removed all references to “i&t” (¹⁷⁷Lu PSMA i&t) when referring to ¹⁷⁷Lu-PSMA therapy in MBS items ZZZZ and YYYY.

The most significant change from the previous ADAR to the item descriptor for administration of lutetium ¹⁷⁷Lu PSMA i&t therapy is splitting treatment, for up to 6 cycles in total, into initial (Table 3; 2 cycles) and continuing treatment (Table 4; 4 cycles). For continuing treatment, only those who have not developed disease progression while receiving ¹⁷⁷Lu PSMA i&t for this condition are eligible. The ADAR states there are separate item descriptors for initial and continuing phases of treatment to ensure appropriate use of ¹⁷⁷Lu PSMA i&t in patients who continue to derive benefit from treatment.

The proposed fee for ¹⁷⁷Lu PSMA i&t remains unchanged from the previous ADAR at \$8,000 per dose, which includes a whole-body Lu PSMA single-photon emission computed tomography (SPECT) 24 hours following each treatment. As noted in the commentary to the previous ADAR, 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; \$93.20) would apply.

Table 3 ADAR 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 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 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%* = \$7,906.80

* 85% benefit reflects the 1 November 2022 Greatest Permissible Gap (GPG) of \$93.20. All out-of-hospital Medicare services that have an MBS fee of \$621.50 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 ADAR. Patients are required to be PSMA-positive as determined by PSMA PET defined as maximum standardized uptake value (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 ADAR proposes the initial phase of treatment constitutes at least 2 cycles of treatment before the assessment of response based on the results from Emmett et al (2023) (the Re-SPECT study, a retrospective analysis of a clinical ¹⁷⁷Lu PSMA i&t treatment program, n= 125). The only rationale provided for limiting initial therapy to two cycles provided in the ADAR states that “Of patients (n=36) that ~~received~~ had PSA or RECIST progression before dose 3 (i.e. response group 3 [Rise in PSA and/or imaging PD; recommended for an alternative treatment], 17 received a subsequent Lu PSMA i&t dose. Of these, none had a treatment response to a subsequent Lu PSMA i&t dose (unpublished data on file – this could not be independently verified).”

Additionally, the item descriptor does not indicate whether assessment of response (or progression) is conducted after each cycle or only after cycle 2. It is also unclear whether response would be assessed immediately after the first or second dose (at weeks 0 and/or 6) or before the subsequent dose (doses 2 and/or 3 at weeks 6 and/or 12).

Table 4 ADAR proposed item descriptor for Lutetium 177 PSMA – continuing phase

Category 3 - Therapeutic Procedures T3. Therapeutic Nuclear Medicine
<p>MBS item YYYY</p> <p>Treatment phase: continuing treatment</p> <p>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:</p> <ul style="list-style-type: none"> • 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 <p>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.</p> <p>A patient is eligible to claim once per cycle up to a maximum of 4 cycles in the continuing treatment phase.</p>
<p>Fee: \$8,000 Benefit: 85%* = \$7,906.80</p>

* 85% benefit reflects the 1 November 2022 Greatest Permissible Gap (GPG) of \$93.20. All out-of-hospital Medicare services that have an MBS fee of \$621.50 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 item descriptor for continuing treatment is limited to those who do not develop disease progression while on treatment with ¹⁷⁷Lu 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 definition of PSA progression provided in the ADAR is not entirely consistent with Prostate Cancer Working Group 3 (PCWG3) definition (≥25% and ≥2ng/mL above the nadir, and which is confirmed by a second value ≥3 weeks later) or the definition used in TheraP (an increase of at least 25% and at least 2 ng/mL after 12 weeks).

It is not clear why there is a criteria of “new soft tissue metastases on diagnostic CT as per RECIST criteria” without assessment of existing sites of metastatic disease. RECIST 1.1 primary focus is on existing target and non-target lesions. Additionally, in both TheraP and VISION, bone scans and clinical progression were also used to assess disease progression. PCWG3 and the National Comprehensive Cancer Network (NCCN) also recommend histology to assess disease progression.

As for the item descriptor for initial treatment, the item descriptor for continuing treatment does not specify how often or when disease progression will be assessed.

Although SPECT/CT post therapy is required after each cycle to confirm ¹⁷⁷Lu uptake at tumour sites, the item descriptor does not specify the role of SPECT/CT to determine the continuation of the treatment.

Additionally, it is unclear what will happen with patients who have complete response, partial response, or stable response and if the type of response will have an impact on the number of treatment cycles. For instance, according to the TheraP study, ¹⁷⁷Lu PSMA-617 treatment could be suspended in the following situations:

1. “The SPECT/CT showed very low or no PSMA uptake at sites of metastatic disease (intensity less than physiological liver activity) on central review” (TheraP, Hofman et al 2021 pp. 798-799).

2. Exceptional response to ¹⁷⁷Lu PSMA-617. “An exceptional response is defined on the 24-h post treatment single-photon emission CT (SPECT)/CT as a marked reduction in uptake at all sites of disease with minimally avid or non-PSMA-avid disease. Patients who subsequently experience disease progression may be considered for re-treatment with ¹⁷⁷Lu PSMA-617” (Clinical Trial Protocol ANZUP 1603, Hofman et al 2019, p.8).
3. Adverse events of severity grade 3–4, with the exception of fatigue or lymphocytopenia, and not restarted until the adverse event has resolved to grade 0–2 (Clinical Trial Protocol ANZUP 1603, Hofman et al 2019, p.8)

In case of treatment suspension patients could recommence ¹⁷⁷Lu PSMA-617 treatment “at symptomatic progression, PSA progression, or radiological progression if patients had received fewer than six cycles and repeat imaging with [⁶⁸Ga]Ga-PSMA-11 and 2-[¹⁸F]FDG PET-CT met the criteria for PET scan eligibility” (TheraP, Hofman et al 2021 p.799; Clinical Trial Protocol ANZUP 1603, Hofman et al 2019, p.8).

Emmett et al 2023 also suggested a break in treatment in case of marked reduction (50% in PSA and imaging-PR) until subsequent PSA rise, then consider re-treatment. Median treatment break was 6.1 months (IQR 3.4-8.7).

Overall the commentary considered:

1. The definition of mCRPC disease progression remains uncertain with respect to the inclusion of clinical progression, histology, and bone lesions assessment.
2. The definition of PSA progression is not entirely consistent with the PCWG3 and NCCN definition.
3. Frequency of diagnostic workup and timing to assess the disease progression is uncertain.

Consideration of whether the item descriptor should specify the following is required:

- the inclusion of Lu PSMA SPECT/CT as one of the criteria for continuing treatment,
- the inclusion of evidence of target and non-target existing soft tissue lesions in addition to the new soft tissue lesions.
- the type of CT imaging,
- criteria of continuing treatment for patients with the exceptional response, especially if they can recommence the treatment on their progression based on the criteria of disease progression for continuing treatment.
- criteria of continuing treatment for patients with complete, partial or stable response.
- criteria of treatment suspension and consequently commencement of treatment.

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 (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:

- ¹⁷⁷Lu PSMA i&t, 7.5-8.5 GBq IVI every 6 weeks for up to 2 cycles (initial)
- ¹⁷⁷Lu 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 ¹⁷⁷Lu PSMA i&t)
- ¹⁷⁷Lu 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 (¹⁷⁷Lu 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 received input from 22 organisations and 25 individuals. For further details see the [1686 Public Summary Document](#).

Additional feedback was received for the current ADAR 1686.1 from 11 organisations, and three (3) consumer organisations (14 organisations in total):

As with the previous feedback received for the 1686 ADAR, all consumer organisations and most other organisations were supportive of the application.

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

- Consumer organisations noted the improved quality of life as the treatment not only extends overall survival and delays treatment progression, but it also results in improvements in pain, fatigue and social functioning. A specialist organisation also noted the proposed treatment has the potential to significantly reduce the intensity of care for the patient and improve the quality of life for the patient's carers and family.
- One consumer organisation noted the proposed treatment would provide accessible and affordable options for patients with few or no other treatments available, allow people with mCRPC to live longer at home and also buy them more time until another treatment may become available in the future.
- A consumer organisation and specialist organisation noted the trials demonstrated efficacy with fewer side effects even in patients who have previously received other treatments, including chemotherapy and androgen receptor-targeted therapies.
- A specialist organisation noted the proposed descriptors for the imaging, initial treatment and ongoing treatments ensure that patients who have appropriate PSMA expression are being treated, and that those who are benefiting from initial treatment will receive ongoing treatment. Men who are not benefiting from the treatment can be identified early and have their management changed to other forms of treatment.

The disadvantages and concerns raised in the consultation feedback for the proposed intervention were:

- Some organisations again raised a concern that there is insufficient high-quality evidence to support the claim of equivalence between ^{177}Lu PSMA i&t and ^{177}Lu PSMA-617, and therefore it is not valid to use studies on ^{177}Lu PSMA-617 to support claims of efficacy and safety for PSMA i&t.
- Some organisations considered the proposed MBS fee per cycle is insufficient for the cost of supply and delivering this agent. A commercial organisation therefore considered there may be significant out of pocket costs for patients or public hospitals, noting that DVA is currently funding patients to receive this treatment at \$10,000 per cycle. Another commercial organisation considered that the proposed fee raised implications for equity of access and additional environmental costs.
- One commercial company again noted that ^{177}Lu PSMA i&t is proposed to be produced under TGA exemption in public hospitals. It considered that this would limit the availability of the service and may result in variable service due to the lack of regulated quality standards and oversight.
- One organisation raised concerns that the proposed accreditation requirements are restrictive and not clinically appropriate.

Other comments raised regarding the proposed interventions were:

- That ^{177}Lu PSMA i&t is a non-GMP non-TGA approved therapeutic agent, and the proposed medical service is made under the TGA exemption which is offered only in public hospitals.
- One organisation noted there is no further substantive data showing the necessity for post-treatment SPECT scans or pre-treatment FDG PET scans, however there is a need for serial PSMA PET imaging in monitoring response to therapy. Another organisation considered 24-hour post treatment SPECT/CT has a role, but is not mandatory for patient benefit.
- One consumer organisation disagreed with the previous MSAC preference for a 5-year time horizon and supported the 7-year horizon proposed for this population, with the suggestion that the economics could be reviewed in 5 years in the light of more mature trial data and real-life experience.
- One consumer organisation considered that ^{177}Lu PSMA i&t therapy could follow unsuccessful second-line chemotherapy on the basis of a more 'acceptable' cost effectiveness.
- Two commercial organisations again raised concern regarding patent issues arising from any manufacture, use or administration of ^{177}Lu PSMA i&t in Australia.

10. Characteristics of the evidence base

No new evidence was presented informing outcomes for comparative safety and effectiveness.

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

11. Comparative safety

The comparative safety was not reconsidered in this ADAR. MSAC previously accepted the high certainty from the evidence that ¹⁷⁷Lu PSMA i&t therapy is acceptably safe.

12. Comparative effectiveness

The comparative effectiveness was not reconsidered in this ADAR. MSAC previously accepted the high certainty from the evidence that ¹⁷⁷Lu PSMA i&t therapy is acceptably effective.

13. Economic evaluation

The ADAR presented a cost-effectiveness/cost-utility analyses (CEA/CUA) using the same partitioned survival model and a proportional hazards approach as in the original ADAR (MSAC 1686). Both models have a cycle length of one week and three health states: progression-free survival (PFS), progressed disease, and death. The underlying logic of the model remained unchanged and includes the application of hazard ratios (HRs) from the TheraP trial to the K-M survival data from the VISION trial and an implicit assumption that the treatment cost applies only to the patients who remain progression-free.

The Applicant stated that in order to align with advice from MSAC and the PBAC, the original model has been re-specified with respect to the following:

1. The model in the current ADAR has a 7.5 year time horizon, despite advice from MSAC that for the proposed population, a time horizon of five years would be more appropriate in the base case model noting that this change [from the longer time horizon of 10 years considered in the previous ADAR] would increase the ICER (MSAC 1686 PSD, p.6).
2. The time on ¹⁷⁷Lu PSMA i&t treatment (ToT) in the model presented in the current ADAR has been changed and is now based on the 3-year PFS data from the Australian TheraP trial, with a mean value now estimated at 3.63 cycles per patient (compared with 4.71 cycles per patient based on VISION PFS in the previous ADAR). The ADAR stated that the use of TheraP PFS data is considered applicable to estimate ToT as it is (a) consistent with the proposed definition of disease progression in the MBS item descriptor (*first introduced in the current ADAR*) and (b) consistent with the median number of 4 treatment cycles observed in Australian clinical practice.
 - Setting aside an incorrect comparison of mean and median values from two different settings, the mean value of ToT is not used in the CEA. Instead, the variable, confusingly titled “time on treatment” or “ToT” is used to calculate the total cost of ¹⁷⁷Lu PSMA i&t treatment. Since the unit cost for ¹⁷⁷Lu PSMA i&t treatment applies ONLY to progression-free patients, there is an implicit assumption that only progression-free patients remain eligible for treatment on a week-by-week basis. This assumption was used in both the original (MSAC 1686) and the revised models. While in the original model ToT was equal to progression-free survival extracted from the graphical representation of the K-M data from the VISION trial, in the revised model the ToT is decoupled from PFS and for the first 36 weeks (the maximum duration of the 6 cycles of treatment) is based on the K-M survival data from the TheraP trial. Importantly, apart from the ToT values used in cost calculation, the rest of the model (i.e. PFS, OS, LYs and QALYs) remains linked to K-M data from the VISION trial for the entire span of the model, starting from week one. This is a violation of model integrity. The evaluators could not find a precedent of a model that incorporates patient-level data from two different trials. This approach reduced the total

cost of treatment by 21%. In comparison to the PFS observed in the larger phase III VISION trial, transition to the progressed disease in the TheraP trial occurs at a higher rate so that by the end of the 36th week, there are 34% of all patients in the PFS state versus the estimated 57% if the VISION data were used for the cost calculation. MSAC noted a marked difference between PFS reported in the ¹⁷⁷Lu PSMA-617 arms in TheraP (5.1 months) versus VISION (8.7 months), however similar radiologic/ radiographic PFS was observed in TheraP (approximately 9 months) compared with 8.7 months in VISION (PSD, p.10). It remains uncertain whether the difference in the rates of disease progression between the trials can be solely explained by the differences in the criteria for establishing progression. MSAC noted that the definition of PFS had implications for the cost-effectiveness and overall cost of listing ¹⁷⁷Lu PSMA i&t on the MBS (MSAC 1686 PSD, p.10).

3. The base case economic analysis has been updated to use the comparator weighting 75% best supportive care /25% cabazitaxel, which aligns with previous PBAC decision for olaparib in advanced prostate cancer.
4. MSAC previously noted that ESC considered the utilities to be appropriate. MSAC also noted (MSAC 1686 PSD, p.5) that in the TheraP trial, patient reported outcomes and quality of life were better with ¹⁷⁷Lu PSMA-617 than cabazitaxel, suggesting that the utility of PFS should be higher with ¹⁷⁷Lu PSMA-617 than cabazitaxel. The model in the current ADAR converted the treatment-agnostic utility value of 0.74, that equally applied to PFS patients in either ¹⁷⁷Lu PSMA i&t or the comparator arm, into two treatment-specific utilities where patients, who received best supportive care but still remained progression-free, attracted a specifically utility value of 0.59, which in the original model applied only to the progressed disease state in both arms of the model. The base-case analysis in the current ADAR (1) reversed the allocation of patients in the comparator arm to 25% cabazitaxel and 75% best supportive care, as suggested by MSAC and (2) differentiated the PFS health state utilities between ¹⁷⁷Lu PSMA i&t and cabazitaxel/best supportive care patients. In fact, both suggestions were combined. The weighted new utility estimate for the PFS in the cabazitaxel/best supportive care arm became 0.62. The utility value for progressed disease (0.59) remained unchanged regardless of the pathway that led to the PD health state.

The reassignment of the previously identified health state-specific utility values to become treatment-specific utility values was not sufficiently justified in the ADAR. A brief ad-hoc literature search was conducted and revealed a complex non-linear relationship between the type of treatment (e.g. chemotherapy), the stage of disease progression, symptoms (adverse events) and quality of life. Apart from the disutility of 0.04 that applied to cabazitaxel patients to reflect its toxicity (i.e. $0.74 - 0.04 = 0.70$), there was no other treatment-specific utility estimate in the proposed population that could be used in the PFS health state with any degree of certainty.

Table 5 Summary of the economic evaluation incorporating the changes made by the Applicant in the ADAR

Component	1686 ADAR	1686.1 ADAR
Perspective	Australian healthcare system	No change
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	No change
Prior testing	PSMA PET/CT	No change
<i>Patient pathway</i>	Treatment with ¹⁷⁷ Lu PSMA i&t is continued for a maximum of 6 cycles but should be ceased if there is evidence of disease progression or unacceptable toxicity however, the termination conditions were removed from the final version of the item descriptor (1686 PSD, Table 2, p.10)	Only the patients who have not developed disease progression after receiving Lutetium ¹⁷⁷ PSMA in the first two cycles are eligible to continue the treatment for up to 6 cycles.
Comparator	Base-case: Weighted comparator of 75% cabazitaxel and 25% BSc. Alternative base-case: Weighted comparator of 25% cabazitaxel and 75% BSc.	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	No change
Outcomes	Cost per life-year gained (cost/LYG) Cost per quality-adjusted life year (cost/QALY)	No change
Time horizon	10 years in the base-case (vs median follow-up of 20.9 months in VISION)	7.5 years in the base-case. <i>The more conservative 5-year time horizon suggested by MSAC may be more appropriate for the proposed population and was tested in sensitivity analysis.</i>
Computational method	Partitioned survival analysis, including proportional hazards approach	No change
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 the model time horizon of 10 years. 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 original ADAR). To model cabazitaxel/BSc outcomes: Proportional hazards approach was adopted whereby hazard ratios for PFS and OS from TheraP and VISION (Hofman 2021, Sartor, 2021a) were applied to the modelled PFS and OS in the ¹⁷⁷ Lu PSMA i&T arm. <i>In particular,</i>	No change in the modelling approach. Hazard ratios for OS [updated to 1.0 from 0.62] and PFS [updated to 0.62 from 0.63] in the cabazitaxel comparator arm were sourced from latest data from the three year follow-up of TheraP (Hofman 2022) provided in the previous application [pre-MSAC response]. <i>Note, HR for the comparator PFS is a weighted sum of HR Lu PSMA-617 + BSc vs BSc (0.40) and Lu PSMA-617 + BSc vs cabazitaxel (0.62). In the current ADAR the base-case HR for the comparator PFS becomes $(0.62*75\%)+(0.40*25\%)=0.565$ (compared with 0.4575 previously)</i>

Component	1686 ADAR	1686.1 ADAR
	<p>Data from VISION (¹⁷⁷Lu PSMA-617) was used to inform PFS and OS of ¹⁷⁷Lu PSMA i&t vs BSc in the model</p> <p>TheraP (¹⁷⁷Lu PSMA-617) was used to inform the PFS of ¹⁷⁷Lu PSMA i&t versus cabazitaxel</p> <p>In the absence of OS data from TheraP to inform the comparative effectiveness of ¹⁷⁷Lu PSMA i&t versus cabazitaxel, the base case assumed the comparative OS benefit for ¹⁷⁷Lu PSMA-617 versus cabazitaxel is the same for ¹⁷⁷Lu PSM-617A versus BSc (i.e. HR=0.62)</p> <p>This value of HR=0.62 was subjected to extensive sensitivity analysis</p>	
Health states	Three health states: progression-free survival, progressed disease and death	No change
Cycle length	1 week	No change
Transition probabilities	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	No change to health state allocation over time approach.
Utilities	Treatment-agnostic utility values used for the health states: PFS - 0.74, progressed disease - 0.59; death- 0	Treatment specific utilities for the PFS health state are applied (Lu PSMA-i&t 0.74; Cabazitaxel/BSc 0.62). <i>Evaluators dispute the choice of treatment-specific utilities, which does not correspond to the structure of the model and is not adequately supported by the clinical evidence.</i>
Costs	2022 costs	Updated to January 2023 costs
Discount rate	5% for both costs and outcomes]	No change
Software	Microsoft Excel	No change

ADAR=applicant developed assessment report; ASI=androgen signalling inhibitor; OS=overall survival; PFS=progression-free survival

The following corrections to the cost calculations were undertaken by the evaluators:

1. Eligibility for continuation with Lu PSMA i&t treatment (referred to as ¹⁷⁷Lu-PSMA in MBS item YYYY) is established after the second cycle. This implies that all the surviving patients, whether in a progressed or a progression-free disease state, are eligible and receiving Lu PSMA i&t treatment for the first 12 weeks. At the moment, as explained above, only PFS patients (following K-M survival data from the latest TheraP follow-up) attract the Lu PSMA i&t treatment unit cost. This was corrected by applying the Lu PSMA i&t treatment unit cost to all surviving patients for the first 12 weeks. Since the latest OS data from the 3-year TheraP follow-up was not presented in the ADAR, the OS from the VISION trial was used to estimate the cost of treatment in the first two cycles. Subsequently, to preserve consistency in the PFS data in the context of a partition survival model, the proportions of progression-free patients eligible for Lu PSMA i&t continuation in the next cycles four, five and six were also obtained from the VISION PFS data. This logical necessity effectively exposed the use of the TheraP PFS data solely for Lu PSMA i&t treatment costing as incompatible with partition-survival modelling that relies on the VISION data for every other outcome.

- The amended item descriptor (MBS item YYYY – continuation) required a diagnostic computerised tomography (CT) scan to establish disease progression (along with a rise in PSA of > 2 ng/mL confirmed by 2 tests a minimum 2 weeks apart). This is a separate CT test, distinct from the whole-body prostate specific membrane antigen [PSMA] positron emission tomography [PET]/[CT] administered at baseline to establish eligibility for initial Lu PSMA i&t treatment. Although not clearly explained in the ADAR, it appears that a CT/bone scan is administered regularly to confirm eligibility for Lu PSMA i&t treatment. In the TheraP trial, CT of the chest, abdomen and pelvis, and technetium-^{99m}-phosphonate bone scan were done every 12 weeks until radiological progression (Hofman, 2021 p.799). However, neither the CT unit cost of \$100 (MBS item 61505) nor the bone scan cost of \$333.55 (MBS item 61446) were utilised in the calculation of the pre-progression disease management cost (the corresponding frequencies were set to zero). These costs were added by the evaluators to the total cost of pre-progression disease management assuming it is conducted every 12 weeks until radiological progression.

Table 6 and Table 7 show results of an economic evaluation as presented in the ADAR.

Table 6 Results of the stepped economic analysis (as in ADAR)

Strategy	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER
Step 1 (cost per LY – 90.8-week time horizon)					
¹⁷⁷ Lu PSMA i&t	\$57,169	\$21,887	1.158	0.135	\$161,960
Cabazitaxel/BSc	\$35,282		1.023		
Step 2 (cost per LY – 7.5-year time horizon)					
¹⁷⁷ Lu PSMA i&t	\$69,003	\$25,690	1.646	0.402	\$63,969
Cabazitaxel/BSc	\$43,313		1.245		
Step 3 (cost per QALY – 7.5-year time horizon)					
¹⁷⁷ Lu PSMA i&t	\$69,003	\$25,690	1.096	0.349	\$73,622
Cabazitaxel/BSc	\$43,313		0.747		

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

Table 7 Base-case incremental costs and effectiveness as presented in the ADAR

Strategy	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (\$/QALY)
¹⁷⁷ Lu PSMA i&t	\$69,003	\$25,690	1.096	0.349	\$73,622
Cabazitaxel/BSc	\$43,313		0.747		

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

As reported above, a number of issues with the economic evaluation presented in the ADAR were identified. The following tables (Table 8 and Table 9) provide analyses testing alternative assumptions in the model:

- Time horizon was set at 5 years, as suggested by MSAC (MSAC 1686 PSD, p.5).
- Cost of ¹⁷⁷Lu PSMA i&t treatment was recalculated as explained above.

3. Cost of pre-progression disease management was amended to include the costs of CT/bone scan administered every 12 weeks until radiological progression.
4. Assumptions about the treatment-specific utility values were reversed and the same utility value of 0.74 was used in the PFS health state in either patients treated with ¹⁷⁷Lu PSMA i&t or best supportive care. Patients treated with cabazitaxel attracted a disutility value of 0.04 that supposed to reflect excessive toxicity of the medication. Whether there is any double counting of disutilities of adverse events observed in cabazitaxel patients is uncertain.

Presentation of the alternative results proceeds as following: at first, each of the four steps above was undertaken separately to produce an alternative ICER estimate (Table 8); secondly, the same steps were performed sequentially along with the cumulative impact on the ICER estimate (Table 9).

Table 8 Commentary sensitivity analyses (Alternative assumptions, tested separately i.e., 1-way SA)

Strategy	Steps	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (\$/QALY)	Impact (%)
¹⁷⁷ Lu PSMA i&t	Base-case in the ADAR #	\$69,003	\$25,690	1.096	0.349	\$73,622	N/A
Cabazitaxel/BSc		\$43,313		0.747			
¹⁷⁷ Lu PSMA i&t	Time horizon 5 years	\$67,939	\$25,020	1.050	0.315	\$79,496	+8.0
Cabazitaxel/BSc		\$42,919		0.735			
¹⁷⁷ Lu PSMA i&t	ToT reversed to survival data from VISION*	\$76,440	\$33,128	1.096	0.349	\$94,936	+29.0
Cabazitaxel/BSc		\$43,313		0.747			
¹⁷⁷ Lu PSMA i&t	Costs of CT/Bone scans added^	\$70,307	\$26,994	1.096	0.349	\$77,347	+5.0
Cabazitaxel/BSc		\$43,313		0.747			
¹⁷⁷ Lu PSMA i&t	Utility cabazitaxel=0.7 BSC=0.74	\$69,003	\$25,690	1.101	0.301	\$85,393	+16.0
Cabazitaxel/BSc		\$43,313		0.8			

Time horizon=7.5; treatment cost is based on the ToT=PFS from the 3-year TheraP follow-up; CT/Bone scan cost=0; BSC utility value=0.59 in both PFS and PD health states.

* The unit cost of Lu PSMA i&t treatment is applied to a) all surviving patients for the first 12 weeks using OS survival data from VISION; b) all progression-free patients from week 13 to week 36 using PFS survival data from VISION.

^ Assumed to be conducted every 12 weeks.

Abbreviations: ToT= time on treatment; BSC=best supportive care; ICER, incremental cost-effectiveness ratio; ¹⁷⁷Lu, lutetium-177; PSMA, prostate specific membrane antigen; QALY, quality-adjusted life year

Table 9 Commentary sensitivity analyses (Alternative assumptions, tested cumulatively i.e., 1-waySA + multivariate SA)

Strategy	Steps	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (\$/QALY)	Impact (%)
¹⁷⁷ Lu PSMA i&t	Base-case in the ADAR#	\$69,003	\$25,690	1.096	0.349	\$73,622	N/A
Cabazitaxel/BSc		\$43,313		0.747			
¹⁷⁷ Lu PSMA i&t	Time horizon 5 years	\$67,939	\$25,020	1.050	0.315	\$79,496	+8.0
Cabazitaxel/BSc		\$42,919		0.735			
¹⁷⁷ Lu PSMA i&t	ToT reversed to survival data from VISION*	\$75,376	\$32,457	1.050	0.315	\$103,127	+40.1
Cabazitaxel/BSc		\$42,919		0.735			
¹⁷⁷ Lu PSMA i&t	Costs of CT/Bone scans added^	\$76,680	\$33,761	1.050	0.315	\$107,271	+45.7
Cabazitaxel/BSc		\$42,919		0.735			
¹⁷⁷ Lu PSMA i&t	Utility cabazitaxel=0.7 BSC=0.74	\$76,680	\$33,761	1.055	0.267	\$126,623	+72.0
Cabazitaxel/BSc		\$43,313		0.788			

Time horizon=7.5; treatment cost is based on the ToT=PFS from the 3-year TheraP follow-up; CT/Bone scan cost=0; BSC utility value=0.59 in both PFS and PD health states.

* The unit cost of ¹⁷⁷Lu PSMA i&t treatment is applied to a) all surviving patients for the first 12 weeks using OS survival data from VISION; b) all progression-free patients from week 13 to week 36 using PFS survival data from VISION.

^ Assumed to be conducted every 12 weeks.

Abbreviations: ToT= time on treatment; BSC=best supportive care; ICER, incremental cost-effectiveness ratio; ¹⁷⁷Lu, lutetium-177; PSMA, prostate specific membrane antigen; QALY, quality-adjusted life year

MSAC noted that there were three key drivers in the previous ADAR economic model. The first was assumed effectiveness in terms of OS of cabazitaxel. The current ADAR used a more conservative OS HR=1 for cabazitaxel from the latest TheraP data thus reducing this uncertainty. The second key driver was extrapolation, where the treatment effect continued beyond 20.9 months in the trial period for up to 10 years [reduced to 7.5 years]. The third key driver was the time horizon, which was 10 years in the base case, and became 7.5 years and no longer a driver of the model (using the cut-off criteria of 15%).

The ICER was most sensitive to the changes in approach to costing of ¹⁷⁷Lu PSMA i&t treatment (see above), followed by utilities. Both key drivers favour ¹⁷⁷Lu PSMA i&t.

The pre-MSAC response presented additional one-way sensitivity and scenario analyses to address the ESC's concerns for using PFS from VISION (¹⁷⁷Lu PSMA-617) to model PFS outcomes in the CEA but PFS from TheraP (¹⁷⁷Lu PSMA-617) to model time on ¹⁷⁷Lu PSMA i&t treatment in the economic model (Table 10).

Table 10 One-way sensitivity analyses

Scenario	Incremental cost	Incremental QALYs	ICER (cost per QALY)	Relative impact to base-case
Base-case	\$25,690	0.349	\$73,622	N/a
Utility cabazitaxel = 0.7 and BSc = 0.74 for PFS health state	\$25,690	0.301	\$85,393	+16.0%
Utility cabazitaxel = 0.7 and BSc = 0.7 for PFS health state	\$25,690	0.314	\$81,901	+11.2%
Utility ¹⁷⁷ Lu PSMA i&t = 0.7 and BSc = 0.59 for PFS health states	\$25,690	0.316	\$81,391	+10.6%

Abbreviations: BSc, best supportive care; ICER, incremental cost-effectiveness ratio; PD, progressive disease; PFS, progression-free survival; QALY, quality adjusted life year

14. Financial/budgetary impacts

The use of health technology in practice presented in the ADAR is based on some changes to the previous ADAR and not a new presentation of the financial impacts. 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 ¹⁷⁷LuPSMA i&t presented in MSAC 1686.1 are summarised in Table 11.

The estimates are derived using the following assumptions:

- the estimated population has been updated to commence in 2023;
- the proportion of patients otherwise treated with cabazitaxel has been changed to 25% from 75% in the previous ADAR;
- average number of ¹⁷⁷Lu PSMA i&t cycles has been reduced to 3.63 cycles compared to 4.7 in the previous ADAR; and
- the cost of cabazitaxel and its administration have been updated to reflect the current January 2023 costs.

Table 11 Net cost to the MBS and R/PBS

Year	2023	2024	2025	2026	2027
Eligible Population	3,043	3,083	3,124	3,165	3,206
Uptake rate	11.5%	12.8%	14.3%	15.9%	17.8%
Number of MBS Services (PSMA PET)	350	395	447	504	570
MBS costs (PSMA PET)	\$416,484	\$470,470	\$531,454	\$600,343	\$678,161
Number of patients treated with Lu PSMA i&t	315	356	402	454	513
MBS costs (Lu PSMA i&t)	\$7,777,745	\$8,785,924	\$9,924,787	\$11,211,274	\$12,664,520
Total cost of PSMA PET and Lu PSMA i&t	\$8,194,228	\$9,256,394	\$10,456,241	\$11,811,617	\$13,342,681
Savings to the MBS and PBS/RPBS from avoided cabazitaxel treatment					
Cabazitaxel administration cost to MBS	\$56,125	\$63,401	\$71,619	\$80,902	\$91,389
Cabazitaxel cost to PBS/RPBS	\$256,478	\$289,724	\$327,279	\$369,702	\$417,624
Net cost to the MBS and RPBS (cost of proposed listing minus savings from cabazitaxel services avoided)					
MBS	\$8,138,103	\$9,192,993	\$10,384,622	\$11,730,714	\$13,251,292
PBS/RPBS	-\$256,478	-\$289,724	-\$327,279	-\$369,702	-\$417,624
Government (MBS + PBS/RPBS)	\$7,881,625	\$8,903,269	\$10,057,343	\$11,361,013	\$12,833,668
<i>Reduction in PBS co-pay included*</i>	\$7,879,436	\$8,900,797	\$10,054,550	\$11,357,857	\$12,830,104
<i>Assume post Lu PSMA i&t use of cabazitaxel 18% + PBS co-pay reduction</i>	\$8,106,086	\$9,156,827	\$10,343,767	\$11,684,564	\$13,199,159
<i>Net Cost to the MBS + (PBS/RPBS) GPG + PBS co-pay \$30</i>	\$9,186,257	\$10,377,012	\$11,722,118	\$13,241,581	\$14,958,003
<i>Net Cost to the MBS + (PBS/RPBS) GPG +cabazitaxel 18% use post Lu PSMA</i>	\$9,412,907	\$10,633,042	\$12,011,335	\$13,568,288	\$15,327,059

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

*From 1 January 2023, the PBS co-payment for non-concession card holders (general patients) was reduced from \$42.50 to \$30.00.

Although the current ADAR now commences in 2023 and not 2022 the assumed uptake remains at 11.5% for the first year, the same as the previous ADAR. As noted at the time, this assumes a very low uptake among this particularly vulnerable group. The ADAR does not elaborate on the reason for the assumed low uptake, apart from expert opinion, with the uptake remaining under 20% of the eligible patients even after five years.

The average net cost per patient is \$25,007 for each of the five years presented. This compares to \$28,627 for the previous ADAR (adjusting for the lower price of cabazitaxel) and reflects the reduced number of cycles of ¹⁷⁷Lu PSMA i&t from 4.71 to 3.63 but offsetting this reduced cost per patient of ¹⁷⁷Lu PSMA i&t is the reduced savings to the PBS/RPBS from the assumption that only 25% of the comparator arm received cabazitaxel, compared to 75% in the previous ADAR and the reduced PBS patient co-pay.

The current ADAR did not include in its calculation of the financial implications the post ¹⁷⁷Lu PSMA i&t use of cabazitaxel, this has been included above. The ADAR assumes that patient co-payment is 15% however given that this intervention is given in an outpatient setting it is likely that the maximum permissible gap applies. As of 1 November 2022, the maximum patient gap between the MBS fee and the benefits payable for out-of-hospital services increased to \$93.20.

The 85% benefit level will apply for all fees up to \$621.50 after which benefits are calculated at the Schedule fee less \$93.20. These changes have been included in the table above.

It remains that the financial implications may be underestimated if the uptake rate is higher than assumed by the current ADAR. Reasons for why the uptake rate would remain under 20% for the eligible population, after five years, for which this is a last resort therapy, were not provided.

15. Other relevant information

Nil.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues: MBS items for therapy

- The ADAR resubmission introduces a new two-step approach to treatment whereby treatment is split into initial (2 cycles) and continuing treatment (4 cycles). The item descriptor has been split into initial and continuing treatment to reflect these changes. MSAC may wish to consider whether this split is appropriate and limiting initial treatment to 2 cycles is justified.
- Only patients who have not demonstrated “disease progression” will be eligible for continuing treatment. In the proposed item descriptor “disease progression” is defined as patients who demonstrate a rise in PSA above a certain threshold and/or show evidence of new soft tissue metastatic disease on diagnostic CT as per RECIST criteria. MSAC may want to consider whether the definition of disease progression in the proposed item descriptor is adequate. In particular, whether: the item descriptor should be expanded to include further evaluation of disease progression such as assessment of existing soft tissue lesions and bone lesion progression, whether additional investigations are required for assessment and to determine which tool is the most appropriate for defining disease progression (RECIST criteria is claimed to not be used in clinical practice).
- There is lack of clarity in the item descriptor regarding when patients should be assessed for response or disease progression. It is unclear if the assessment of response, or progression would occur after each treatment dose or only after the second dose. MSAC is asked to consider the appropriate intervals for the timing and frequency of tests to assess whether “disease progression” or treatment response has occurred.
- The evidence to support effectiveness and improved quality of life of a “treatment holiday” in patients that show early and favourable response to treatment is limited (Re-SPECT study). MSAC is asked to consider whether the proposed items should allow breaks in treatment (i.e. “treatment holidays”).

Economic issues:

- Although some of the previous sources of uncertainty have been addressed, new sources of uncertainty have been introduced. Overall, the ICER remains uncertain and is likely to be higher than the base-case estimate, with the most material issues relating to the use of different trial data sources for the determination of the PFS benefits and treatment costs of ¹⁷⁷Lu PSMA, and the use of treatment-specific utility weights, both of which favour the intervention. MSAC is asked to consider if the uncertainty has been reduced sufficiently to enable reconsideration of its previous advice.

Financial issues:

- The financial impacts presented in the ADAR are likely to be underestimated primarily due to a likely higher uptake rate than assumed for an efficacious therapy that will be used last-line.

ESC discussion

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

- 1) ¹⁷⁷Lu PSMA therapy 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 ¹⁷⁷Lu PSMA i&t is a targeted radionuclide radiotherapy that enters the cancer cell via the PSMA receptor, which is overexpressed in prostate cancer, with expression increasing in metastatic and castrate resistant disease. Therapy is intended for patients with progressive mCRPC after the disease has progressed despite chemotherapy. Testing with PSMA PET and fluorodeoxyglucose PET determines if the patient has an adequate level of the PSMA “target” at all sites of measurable disease such that they will be expected to derive significant benefit from the treatment.

The previous application (1686) was considered by MSAC at its July 2022 meeting. At that time, MSAC acknowledged the high clinical need for this population with advanced disease, and the consumer preference for ¹⁷⁷Lu PSMA therapy over its comparators of best supportive care and cabazitaxel. MSAC noted the limitations in the evidence comparing ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 products but concluded from the evidence available that these two products are mutually noninferior and thus considered the evidence for ¹⁷⁷Lu PSMA-617 to be relevant for ¹⁷⁷Lu PSMA i&t. MSAC accepted the high certainty from the evidence that ¹⁷⁷Lu PSMA i&t therapy is safe and effective but did not recommend listing as the incremental cost-effectiveness ratio (ICER) was too high and uncertain.

ESC noted that the comparative safety and effectiveness were not reconsidered in this ADAR resubmission, rather the resubmission seeks to address the previous MSAC concerns related to the economic evaluation.

ESC noted that the current ADAR differed from the previous ADAR in that it now proposes a two-step approach to treatment. Patients deemed eligible for ¹⁷⁷Lu PSMA will receive an initial two cycles and will only continue treatment (up to four treatment cycles) if there is evidence by the second cycle that the treatment is effective for that patient. The ADAR has proposed separate item descriptors for initial and continuing phases of treatment to ensure appropriate use of ¹⁷⁷Lu PSMA i&t in patients who continue to derive benefit from treatment. ESC noted that the rationale for this approach is based on the results from the Re-SPECT study³, which demonstrated that patients that had disease progression based on PSA rise or RECIST criteria after 2 doses of ¹⁷⁷Lu PSMA failed to derive a subsequent treatment response to additional ¹⁷⁷Lu PSMA treatment. ESC considered it reasonable that a minimum of two treatments would be required to determine if there was a therapeutic benefit. However, 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

³ Emmett L 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.

VISION and TheraP trials. MSAC may wish to consider whether this split is appropriate and limiting initial treatment to 2 cycles only is justified.

ESC noted that in the pre-ESC response the applicant proposed the definition of disease progression in the item descriptor for continuing treatment should be amended to “increase of serum PSA of at least 25% and at least 2 ng/mL after 12 weeks” and remove “and/or evidence of new soft tissue metastases on diagnostic CT as per RECIST criteria”. ESC noted that the proposed item descriptor only refers to progression in terms of new lesions, without making reference to existing lesions or including the assessment of existing soft tissue lesions (in addition to new soft tissue metastases), histology or bone lesion progression. ESC noted that collectively, although the clinical guidelines recommend a variety of investigative tools (CT, bone scans, ultrasound, etc) to assess progression, all include reference to existing lesions to determine whether they are growing significantly. The pre-ESC response agreed that the RECIST criteria is widely adopted in clinical trials but its use for determining soft tissue metastases is less common in clinical practice, and thus considered it clinically appropriate to omit the reference to RECIST criteria if deemed appropriate by MSAC. ESC queried whether the RECIP 1.0 might be the more appropriate criteria to define disease progression, and whether additional investigations may be required to assess disease progression, for example to assess existing soft tissue lesions and bone lesion progression. The applicant’s pre-ESC response considered including additional criteria to the item descriptor for continuing treatment would be too prescriptive and restrictive and requiring additional tests would significantly increase the cost of ¹⁷⁷Lu PSMA treatment. ESC requested MSAC consider whether the item descriptor should be expanded to include further assessment of disease progression, for example through assessment of existing soft tissue lesions and bone lesion progression. MSAC may also wish to consider whether additional investigations, apart from PSA and CT as suggested by the applicant, are required to determine continuation of treatment.

ESC noted that there is lack of clarity in the item descriptor regarding when patients should be assessed for response or disease progression. Although the item descriptor for initial treatment includes ¹⁷⁷Lu PSMA SPECT/CT after each treatment dose, the frequency and timing of other tests to assess disease progression (eg. PSA) are not detailed. It is unclear if the assessment of response would occur after each treatment dose or only after the second dose, when decisions regarding continuing treatment are made. ESC noted it was unclear if patients would be assessed immediately after the first (i.e. week 0) or second dose (i.e. at 6 weeks after the first dose) or just prior to the subsequent dose (i.e. for doses 2 and/or 3 at 6 and/or 12 weeks after the first dose) to determine response. MSAC may wish to consider the most appropriate intervals for the timing and frequency of assessment tests.

ESC noted that the Re-SPECT study included a cohort of men (35% of the total study population) who demonstrated an early and marked improvement following treatment, based on their 6 week SPECT/CT and PSA response. They were able to have a break in treatment (a “treatment holiday”), of median 6.1 months (interquartile range [IQR] 3.4, 8.7), and continued to demonstrate a longer time to disease progression and overall survival. Re-treatment occurred at first subsequent rise in PSA. ESC noted these patients may benefit from improved quality of life due to reduced exposure to the adverse effects of treatment and this approach may lead to lower costs associated with reduced utilisation of the intervention and thus possibly improved cost-effectiveness. However, ESC considered it unclear if there was enough evidence to support “treatment holidays”. ESC considered it unclear if the proposed items should allow for “treatment holidays” for patients who demonstrate an early and favourable response to treatment.

ESC noted that the proposed fee for ¹⁷⁷Lu PSMA i&t remains unchanged from the previous ADAR at \$8,000 per dose, which includes a whole-body Lu PSMA single-photon emission computed tomography (SPECT) 24 hours following each treatment.

ESC noted that consultation feedback was received from a single consumer group, who were supportive of the application. They stated that the benefits of the proposed treatment would be to provide accessible and affordable options for patients with few or no other treatments available, and to allow people with mCRPC to live longer at home and also buy them more time until another treatment may become available in the future.

ESC noted the economic model used the same partitioned survival model and a proportional hazards approach as in the previous ADAR. The cost-effectiveness analysis was updated taking into account some of the previous feedback from MSAC, the updated MBS items for therapy, further information on time to treatment (ToT) and response to therapy, time horizon and comparator weighting. The base-case analysis in the current ADAR derived an ICER for ¹⁷⁷Lu PSMA i&t vs cabazitaxel/best supportive care at \$73,622 per quality-adjusted life-year (QALY). ESC noted the progression-free survival (PFS) data (referred to as ToT) from the TheraP trial used exclusively for ¹⁷⁷Lu PSMA i&t treatment costing proved to be a major driver for the lower ICER estimate in the ADAR compared to the previous ICER of \$81,653/QALY. The second largest contributor was the new treatment-specific utility values.

ESC noted the additional one-way sensitivity analyses presented in the commentary:

- The time horizon was set at 5 years, as suggested by MSAC previously.
- The cost of ¹⁷⁷Lu PSMA i&t treatment was recalculated using the ToT from the VISION trial data.
- The cost of pre-progression disease management was amended to include the costs of CT/bone scan administered every 12 weeks until radiological progression. ESC queried whether these are incremental costs associated with the intervention or already part of standard clinical practice. ESC noted the impact of including these costs on the ICER to be moderate.
- Assumptions about the treatment-specific utility values were reversed and the same utility value of 0.74 was used in the PFS health state in either ¹⁷⁷Lu PSMA i&t or best supportive care patients. Cabazitaxel patients attracted a disutility value of 0.04 that was supposed to reflect higher toxicity of the medication. Whether there is any double counting of disutilities of adverse events observed in cabazitaxel patients is uncertain. ESC considered that while a disutility for cabazitaxel was acceptable, the assumed approach of applying treatment-specific utility values favoured the intervention. In particular, ESC noted that applying the same utility values for best supportive care in the PFS and PD health states may not have been reasonable.

ESC noted the pre-ESC response acknowledged that modelling ¹⁷⁷Lu PSMA i&t treatment costs using ToT based on TheraP data was inconsistent with the modelling of PFS and OS outcomes based on data from VISION. The applicant claimed this approach to be more reflective of the proposed use and expected ToT of ¹⁷⁷Lu PSMA i&t in Australian clinical practice (given the alignment with the proposed continuation criteria in the item descriptor). ESC considered that the use of different trial data for determination of PFS benefits and costs favoured the intervention and was a key source of uncertainty.

ESC noted that pre-ESC response justified the 7.5 year time horizon based on the interpretation that a plateau was reached (for ¹⁷⁷Lu PSMA-617) in OS reported in LuPIN, TheraP and VISION as well as the comparatively more mature data for TheraP compared to PROfound (olaparib) where a 7.5-year time horizon was considered by PBAC (Olaparib PSD, November 2021)⁴. ESC considered that the interpretation of reaching the plateau may not have been justified given that low remaining numbers at risk were a source of substantial uncertainty. ESC considered the change in time horizon was more material in the current submission than in the case of Olaparib,

⁴ Olaparib PSD November 2021 PBAC Meeting

noting that reducing the horizon to 5 years has a moderate impact on the base-case ICER. While agreeing with the MSAC's preference for a 5-year horizon, ESC noted that in practice both horizons could be taken into consideration.

ESC noted that the multivariate sensitivity analysis conducted by the commentary resulted in an ICER of \$126,623/QALY and considered that this may represent a conservative case. ESC noted the applicant's view expressed in the pre-ESC response that the combined multivariate sensitivity analysis presented by the commentary represented a highly implausible scenario that was not reflective of the proposed listing in Australian clinical practice.

ESC noted that although some of the previous sources of uncertainty had been addressed, new sources of uncertainty have been introduced. Overall, ESC considered the ICER remained uncertain and was likely to be higher than the base-case estimate.

ESC noted that the financial implications in the current ADAR use the same approach as that used in the previous ADAR, with some changes:

- the estimated population has been updated to commence in 2023
- the proportion of patients otherwise treated with cabazitaxel has been changed to 25% from 75% in the previous ADAR
- average number of ¹⁷⁷Lu PSMA i&t cycles has been reduced to 3.63 cycles per patient based on the 3-year PFS data from the Australian TheraP trial, compared with 4.71 cycles based on VISION PFS in the previous ADAR.
- the cost of cabazitaxel and its administration have been updated to reflect the current January 2023 costs.

The financial impact to the MBS was estimated in the ADAR at \$8,138,103 in 2023, increasing to \$13,251,292 in 2027.

However, ESC noted that some changes requested by MSAC for the previous ADAR have not been included:

- changing the uptake rate from 11.5% to 15% (the applicant considered this scenario as the maximum uptake rate for Lu PSMA i&t in the previous ADAR)
- the post-¹⁷⁷Lu PSMA i&t cabazitaxel use of 18%
- financial implications due to changes to the MBS Greatest Permissible Gap (GPG) and PBS co-pay reduction.

Based on these changes, additional analyses presented in the commentary estimated the financial impact to the government (MBS + PBS/RPBS) to be \$9,412,907 in 2023 to \$15,327,059 in 2027. ESC considered that the budget impact updated in the commentary was still likely to be underestimated primarily due to the uptake rate likely being higher than the 11.5% which these results represented. The additional impact of assuming a 15% uptake rate was previously presented in the PSD for 1686.

17. Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)