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National Health Care Institute
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205005754

Our reference
2025005754

Date 12 March 2025
Re: Package advice lock procedure medicinal product lutetium vipivotide tetraxetan, ^{177}Lu-PSMA-617 (Pluvicto®) for prostate cancer

Dear Ms Agema,

The National Health Care Institute recommends that you evaluate Lutetium (^{177}Lu)-vipivotide tetraxetan, hereinafter ^{177}Lu-PSMA-617 (Pluvicto®) for the treatment of certain patients with metastatic castration-resistant prostate cancer. This advice was prompted by the placement of ^{177}Lu-PSMA-617 in the package lock for expensive medicinal products.

Condition

In the Netherlands, approximately 13,000 men are diagnosed with prostate cancer every year. Prostate cancer usually progresses slowly and does not show any obvious symptoms or problems at first. In cases of metastatic prostate cancer, the chance of survival decreases significantly. The 10-year survival rate of Dutch patients with localised prostate cancer at diagnosis is more than 90%, but in metastatic prostate cancer, the 10-year survival rate falls to 31%. Hormone therapy is often given at the beginning of treatment when the prostate carcinoma is still hormone-sensitive. By decreasing testosterone levels, tumour growth decreases. If tumour growth no longer responds adequately to hormone treatment, this is called castration-resistant prostate carcinoma. Patients are usually treated with chemotherapy (docetaxel or cabazitaxel), an androgen receptor pathway inhibitor (ARPI: enzalutamide, abiraterone, darolutamide) or best supportive care.

Registered indication

^{177}Lu-PSMA-617 (Pluvicto®) in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) treated with AR pathway inhibition and taxane-based chemotherapy.

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Claim by the marketing authorisation holder
In the registered indication, ^{177}Lu-PSMA-617 (Pluvicto®) in combination with ADT has an added value compared to:

- Cabazitaxel for patients treated with ARPI and with one taxane-based chemotherapy who are subsequently eligible for a second taxane-based chemotherapy; and
- Best supportive care for patients treated with ARPI and either two taxane-based chemotherapies or one taxane-based chemotherapy who are no longer eligible for cabazitaxel therapy.

Package advice
The National Health Care Institute has determined that ^{177}Lu-PSMA-617 in combination with ADT meets the legal criterion of 'established medical science and medical practice' in the treatment of adult patients with PSMA-positive metastatic castration-resistant prostate cancer.

- In patients who have been treated with ARPI and one taxane-based chemotherapy who are subsequently eligible for a second taxane-based chemotherapy, there is a similar value to cabazitaxel. For this group, the National Health Care Institute therefore recommends that ^{177}Lu-PSMA-617 be included in the basic healthcare package, provided that the net price after successful price negotiations does not exceed the net price of cabazitaxel.
- In patients treated with ARPI and either two taxane-based chemotherapies or with one taxane-based chemotherapy who are no longer eligible for cabazitaxel treatment, there is an added value over best supportive care. For this group, the National Health Care Institute therefore recommends that ^{177}Lu-PSMA-617 be included in the basic healthcare package, provided that the price can be significantly reduced after successful price negotiations. The cost-effectiveness is very unfavourable based on the available data. On the basis of the cost-effectiveness analysis, a price reduction of 90% should be negotiated. However, the National Health Care Institute recommends taking into account the price of the pharmacy preparation of lutetium (^{177}Lu-PSMA-I&T), which is reimbursed care, and possible competition from other lutetium-containing treatments from 2026 onwards.

We explain the preparation of this package advice below.

General
At your request, the National Health Care Institute assesses whether care should be part of the standard health insurance package from the perspective of the health insurance package paid from joint premiums.

The National Health Care Institute assesses on the basis of the four package

criteria[1]: effectiveness[2]cost-effectiveness[3], necessity[4] and feasibility[5]. The Scientific Advisory Board (WAR) advises the National Health Care Institute on the (scientific) basis and the conclusion of the assessment. If there are risks regarding the accessibility and affordability, the assessment of the package criterion of effectiveness (established medical science and medical practice) will be placed in the wider societal context of the four package criteria. The Insured Package Advisory Committee (ACP) advises the Executive Board of the National Health Care Institute in this regard. This societal weighting results in the package advice. Stakeholders are consulted during the process.

Comprehensive weighting of package criteria

Background

Patients with metastatic castration-resistant prostate cancer who have already received docetaxel (taxane-based chemotherapy) and ARPI (enzalutamide, abiraterone, darolutamide) in a previous line are currently usually treated with cabazitaxel (taxane-based chemotherapy). Patients who are no longer eligible for a second taxane-based chemotherapy, or who have already been treated with two taxane-based chemotherapies, are usually treated with best supportive care. Treatment options also exist for specific sub-populations: olaparib for BRCA-mutations, radium-223 in case of bone metastases only, and the unregistered pharmacy preparation of ^{177}Lu-PSMA-I&T in the absence of a better therapeutic option.

In consultation with the relevant professional associations, three different patient groups have been defined that can be treated with ^{177}Lu-PSMA-617:

- **Group 1**: after treatment with an ARPI and one taxane-containing chemotherapy for patients eligible for cabazitaxel therapy;
- **Group 2**: after treatment with ARPI and one taxane-containing chemotherapy for patients not eligible for cabazitaxel therapy;
- **Group 3**: after treatment with an ARPI and two taxane-containing chemotherapies (i.e. docetaxel and cabazitaxel).

For group 1, the National Health Care Institute considers cabazitaxel as standard treatment and for groups 2 and 3 best supportive care. Due to the limited use of olaparib, radium-223 and ^{177}Lu-PSMA-I&T in specific sub-populations, the assessment did not compare all of these treatment options for pragmatic reasons.

Established medical science and medical practice

Group 1: comparison with cabazitaxel

The effectiveness and safety of ^{177}Lu-PSMA-617 versus cabazitaxel was investigated in an open-label, randomised, controlled phase II study (TheraP). With a median follow-up duration of 35.7 months, there was no clinically relevant

[1] Real-world package management 4 (2023). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[2] Assessment of the established medical science and medical practice (2023). National Health Care Institute. Via www.zorginstituutnederland.nl.

[3] Cost-effectiveness Report (2015)

[4] Necessity is related to both the medical need due to the severity of a disease for the patient (burden of disease) and the need to insure something. See the report on real-world package management 4 (2023).

[5] The package criterion of feasibility deals with whether it is feasible or sustainable to include a specific form of care in the basic healthcare package. It is therefore mainly a test of a number of implementation aspects such as the healthcare organisation, support, ethical and legal aspects, budget impact and so on. See the report on real-world package management 4 (2023).

longer survival. Quality of life also did not show a clinically relevant difference between the two treatments. Grade 3-4 adverse events were less common with ^{177}Lu-PSMA-617 treatment compared to cabazitaxel, but this did not result in a difference in the number of patients who discontinued treatment due to these adverse events.

The National Health Care Institute, advised by the Scientific Advisory Board (WAR), has concluded that ^{177}Lu-PSMA-617 is equivalent to standard cabazitaxel treatment for this indication.

Group 2+3: comparison with best supportive care
The evidence of the effectiveness and safety of ^{177}Lu-PSMA-617 versus best supportive care is based on the open-label, randomised, controlled phase III VISION study, in which 177Lu-PSMA-617 was added to best supportive care compared to best supportive care alone. At a median follow-up duration of approximately 20 months, the median survival was clinically relevant longer in the ^{177}Lu-PSMA-617 group compared to the control group based on the PASKWIL2023 criteria. Quality of life showed no clinically relevant difference between the ^{177}Lu-PSMA-617 treatment arm and the control arm. There is a clinically relevant increase in the incidence of intervention-related serious adverse events and the percentage of patients who discontinued treatment due to adverse events. Because there has been a comparison with best supportive care, this is to be expected and therefore acceptable.

There is uncertainty about the effects found in the VISION study, because there is a high rate of discontinuation in the control arm, the study population is heterogeneous and also not entirely in line with Dutch practice.

The National Health Care Institute, advised by the WAR, has concluded that ^{177}Lu-PSMA-617 has an added value over standard treatment with best supportive care for these indications.

Cost-effectiveness
Due to the therapeutic comparable value of ^{177}Lu-PSMA-617 versus cabazitaxel in group 1, the National Health Care Institute did not evaluate the cost-effectiveness for this group. Because of the added value compared to best supportive care in groups 2 and 3, the National Health Care Institute has assessed the cost-effectiveness for these groups.

The cost-effectiveness analysis of the marketing authorisation holder has been too optimistic, according to the National Health Care Institute. The National Health Care Institute considers that adjustments to the extrapolations, utility values and costs of follow-up and simultaneous treatments are necessary to arrive at analyses of sufficient quality that can be used for decision-making. The cost-effectiveness estimation of this analysis, adjusted by the National Health Care Institute, is above the reference value considered relevant for this condition. ^{177}Lu-PSMA-617 is therefore not cost-effective. The ICER is €436,725 per QALY for group 2 and €506,684 per QALY for group 3. At a reference value of €80,000, the price of ^{177}Lu-PSMA-617 would have to be reduced by 90% to be cost-effective.

Pharmacy preparation
In the Netherlands, a pharmacy preparation of lutetium (^{177}Lu-PSMA-I&T) has

been available for a number of years for patients with metastatic castration-resistant prostate cancer who no longer have other treatment options. This is a different form of lutetium than ^{177}Lu-PSMA-617. ^{177}Lu-PSMA-I&T is currently being reimbursed for patients with metastatic castration-resistant prostate cancer in the absence of better therapeutic options. Important to note is that ^{177}Lu-PSMA-I&T is not a registered product, which means that other quality requirements apply, compared to the registered ^{177}Lu-PSMA-617. Also, no clinical studies have been conducted to evaluate the effectiveness of ^{177}Lu-PSMA-I&T on hard outcomes such as survival in patients with metastatic castration-resistant prostate cancer treated with ARPI and at least one taxane-based chemotherapy. The joint European Association of Nuclear Medicine and American Society of Nuclear Medicine guidelines state that the pharmacokinetics and dosimetry of ^{177}Lu-PSMA-I&T are similar to those of ^{177}Lu-PSMA-617. Based on this and on the TheraP study of ^{177}Lu-PSMA-617, the healthcare insurers have assessed that ^{177}Lu-PSMA-I&T can be reimbursed. ^{177}Lu-PSMA-I&T is available in some hospitals. At present, it does not appear possible to treat all patients eligible for lutetium with the pharmacy preparation. ^{177}Lu-PSMA-I&T costs €33,728 per patient per treatment of 4 (8-week) cycles and is therefore cheaper than treatment with ^{177}Lu-PSMA-617 which costs approximately €87,570 per patient per treatment of 4.5 (6-week) cycles.

Budget-impact analysis
The National Health Care Institute estimates that 1,033 patients per year will be treated with ^{177}Lu-PSMA-617 for metastatic castration-resistant prostate cancer in year 3 after inclusion in the package. The total cost per patient per treatment comes to €87,570. This results in macro costs of €90 million in the third year. When also taking into account cabazitaxel substitution and the pharmacy preparation of lutetium (^{177}Lu-PSMA-I&T), the budget impact will reach €70 million in year 3. This assumes treatment costs of €19,446 per patient for cabazitaxel and €33,728 per patient for ^{177}Lu-PSMA-I&T.

There is a lot of uncertainty about patient numbers. Two scenario analyses have therefore varied the assumptions about these patient numbers, resulting in a budget impact of €61 to €100 million in year 3.

Social weighting (ACP advice)
The Insured Package Advisory Committee (ACP) considers it important that ^{177}Lu-PSMA-617 be made available for the treatment of adult patients with metastatic castration-resistant prostate cancer for whom no other treatment options are possible. The commission recommends that ^{177}Lu-PSMA-617 should not be included in the basic healthcare package, unless a price negotiation results in a significant decrease in the asking price. An annual price at the current pricing level for hospital preparations would be desired from a social perspective. The commission recommends that this be taken into account in the price negotiations. The commission is aware that this will maintain ineffective care, and therefore recommends a price arrangement for a maximum duration of two years because of the expected indication expansions for this product and given the constantly changing treatment landscape.

In conclusion, the National Health Care Institute recommends that you include ^{177}Lu-PSMA-617 for the above indication in the health insurance package, provided that the net price decreases sufficiently after successful price negotiations, as described above.

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Should you need any further information, please do not hesitate to contact us. The assessment reports have been added as annexes (pharmacotherapeutic report, budget-impact analysis, pharmaco-economic report).

Yours sincerely,

M.J. Janssen
Chairperson of the Executive Board