NCPE Assessment

Technical Summary

Lutetium (^{177}Lu) vipivotide tetraxetan (Pluvicto®)

HTA ID 23002

August 2024

Applicant: Novartis Ireland Ltd

Lutetium (^{177}Lu) vipivotide tetraxetan (Pluvicto®) in combination with androgen deprivation therapy with or without androgen receptor pathway inhibition for the treatment of adult patients with progressive prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of ^{177}Lu vipivotide tetraxetan (Pluvicto®).

Following assessment of the Applicant's submission, the NCPE recommends that ^{177}Lu vipivotide tetraxetan (Pluvicto®) not be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Novartis Ireland Ltd) Health Technology Assessment of ^{177}Lu vipivotide tetraxetan (Pluvicto®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In July 2023, the Applicant (Novartis Ireland Ltd) submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of Lutetium (^{177}Lu) vipivotide tetraxetan (Pluvicto®) in combination with androgen deprivation therapy (ADT) with or without androgen receptor pathway inhibition for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy. Novartis Ireland Ltd. is seeking reimbursement of ^{177}Lu vipivotide tetraxetan on the Oncology Drug Management System.

The active moiety of Pluvicto® is the radionuclide ^{177}Lu which is linked to a small-molecule ligand that targets and binds with high affinity to PSMA, a transmembrane protein that is highly expressed in prostate cancer, including mCRPC. Upon the binding of Pluvicto® to PSMA-expressing cancer cells, the beta-minus emission from ^{177}Lu delivers therapeutic radiation to the targeted cell, as well as to surrounding cells, and induces DNA damage which can lead to cell death. The recommended treatment regimen is 7,400 megabecquerels (MBq) intravenously once every six weeks for up to a total of six doses (or less if there is disease progression or unacceptable toxicity).

Current treatment options in Ireland are: cabazitaxel in combination with standard of care (SoC) in the patient population eligible for further taxane treatment (following previous treatment with docetaxel), or standard of care (SoC) only in the patient population not eligible for further taxane treatment. SoC includes, ADT, androgen receptor pathway inhibitors (ARPIs), pain medication, radiation therapy, corticosteroids and bone-targeted agents. Clinical opinion to the Review Group suggests that Radium-223 is a relevant comparator in the subpopulation of patients with symptomatic bone metastases and no extensive visceral metastases.

1. Comparative effectiveness of ^{177}Lu vipivotide tetraxetan

The efficacy and safety of ^{177}Lu vipivotide tetraxetan was assessed in the VISION trial. This was a phase III, international, open-label, randomised controlled trial in men with progressive PSMA-positive mCRPC who were previously treated with one to two taxane-based chemotherapy regimens and at least one ARPI (e.g., abiraterone or enzalutamide). Participants were randomised in a 2:1 ratio to receive either ^{177}Lu vipivotide tetraxetan for up to six cycles plus SoC (n=551), or SoC only (n=280). SoC included ADT, ARPIs, corticosteroids, radiation therapy and bone-targeted agents. Castrate testosterone levels had to be maintained throughout the trial. Participants continued randomised treatment until evidence of tumour progression (based on investigator assessment), unacceptable toxicity, use of prohibited treatment, non-compliance or withdrawal, or lack of clinical benefit. The alternate primary endpoints in VISION were overall survival (OS) and radiographic progression-free survival (PFS) as determined by blinded independent central review. OS was measured in the full analysis set (FAS), comprising all randomised participants. PFS was measured in a subgroup of participants, who had undergone randomisation on or after 5th March 2019, referred to as the progression-free survival full analysis set (PFS-FAS). The reason for the PFS-FAS was because there was a high early dropout rate amongst those randomised to SoC only. Trial site education measures were introduced on the 5th March 2019 to address this issue.

A total of 831 participants underwent randomisation (FAS) with 581 participants being randomised on or after 5th March 2019 (PFS-FAS). The percentage of participants in the SoC only arm who discontinued the trial without receiving the assigned treatment was 56% (47 of 84 participants) before the implementation of the trial site education measures on the 5th March 2019 and 16.3% (32 of 196 participants) after implementation of the measures, as compared with 1.2% (2 of 166 participants) and 4.2% (16 of 385 participants), respectively, in the ^{177}Lu vipivotide tetraxetan arm. Demographic and baseline disease characteristics were balanced between the treatment arms and analysis sets. In the FAS the median age was 71 years (range: 40 to 94 years); 86.8% of participants were white and 92.4% had ECOG Performance Status of 0-1.

Compared with SoC only, treatment with ^{177}Lu vipivotide tetraxetan plus SoC resulted in a statistically significant improvement in both radiographic PFS (median: 8.7 months vs 3.4

months, hazard ratio (HR): 0.40, 95% confidence interval (CI) 0.29 to 0.57, p< 0.001) and OS (median 15.3 months vs 11.3 months, HR: 0.62; 95% CI 0.52 to 0.74, p < 0.001).

The Review Group note concerns with the VISION trial including: a substantial risk of bias from the high rate of study discontinuations among participants in the SoC only arm prior to receiving the randomly assigned treatment; a high level of missing data for treated participants in the SoC only arm (likely to lead to an overestimate of the benefit of ^{177}Lu vipivotide tetraxetan particularly for PFS); treatment decisions on the use of ARPIs were frequently taken post randomisation **(**the impact of concomitant ARPIs cannot be reliably assessed).

The Review Group note that the main active comparator of interest in Ireland (cabazitaxel), was not included in the SoC only arm. Also, the population in VISION is not fully reflective of the population who would be eligible for cabazitaxel in Irish clinical practice. The Applicant is proposing that ^{177}Lu vipivotide tetraxetan will be used as an alternative to cabazitaxel in patients eligible for further taxane treatment, but in fact 38% of participants in VISION had already received cabazitaxel.

The Applicant conducted a network meta-analysis (NMA) comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel and other relevant comparators. Outcomes were reported for OS and PFS. The NMA is limited due substantial heterogeneity, the inclusion of studies in ARPI-naïve populations, the impact of missing VISION data and the lack of genuine randomisation in the 'ARPI at baseline' subgroup of VISION used to connect the network. The Review Group also had concerns with the exclusion of the TheraP randomised controlled trial from the network as this is the only study providing direct comparative evidence on ^{177}Lu vipivotide tetraxetan versus cabazitaxel. The Applicant did not consider this study to provide sufficiently robust evidence for use in the submission. The Applicant also conducted an unanchored indirect treatment comparison (ITC) to compare OS for ^{177}Lu vipivotide tetraxetan versus cabazitaxel, by combining data from VISION with real-world data on cabazitaxel from UK clinical practice using propensity score weighting to balance relevant patient characteristics where possible. This ITC is associated with bias due to residual confounding, as well as from differences in study populations and characteristics between the VISION and UK real-world data sources.

The Review Group requested that the Applicant conduct an alternative NMA ('NCPE alternative NMA') for the outcomes of OS and PFS. This NMA consisted of three-study loop formed by VISION, CARD and TheraP (i.e., studies in ARPI-naïve participants were excluded). This network is considered by the Review Group to have lower heterogeneity and to more closely match the target population compared with the Applicant's NMA and unanchored ITC. Nonetheless, there is still a substantial degree of heterogeneity between the studies included in the NCPE alternative NMA, and the results are considered to be highly uncertain.

Results from the indirect comparisons are presented in Table 1. While the Applicant's NMA and unanchored ITC indicate an OS benefit from ^{177}Lu vipivotide tetraxetan versus cabazitaxel, the NCPE alternative NMA demonstrates approximately equivalent OS between the two treatments. However, all indirect treatment comparisons are limited, and it is not possible to determine the most reliable comparative evidence. Furthermore, while the various indirect comparisons do consistently indicate a PFS benefit for ^{177}Lu vipivotide tetraxetan over cabazitaxel, the magnitude of this benefit is highly uncertain.

Table 1: Results of comparative-effectiveness analysis

	HR (95% CrI) for ^{177}Lu vipivotide tetraxetan vs cabazitaxel	
	OS	**PFS**
Applicant's NMA[a]:	0.60 (0.44, 0.83)	0.48 (0.33, 0.71)
Unanchored ITC[b]	0.76 (0.64, 0.90)	N/A
NCPE alternative NMA	0.99 (0.68, 1.44)	0.65 (0.47, 0.92)

NMA: network meta-analysis; HR: hazard ratio; CrI: credible interval; OS: overall survival; PFS: progression-free survival;
[a] Used to derive treatment effects for cabazitaxel for the PFS outcome only in the Applicant's base case cost-effectiveness model
[b] Used to derive treatment effects for cabazitaxel for the OS outcome in the Applicant's base case cost-effectiveness model

2. Safety of ^{177}Lu vipivotide tetraxetan

In the VISION trial, 529 participants received at least one dose of 7,400 MBq of ^{177}Lu vipivotide tetraxetan (median number of doses was five). The most common adverse reactions include: fatigue (43.1%), dry mouth (39.3%), nausea (35.3%), anaemia (31.8%), back pain (23.4%), arthralgia (22.3%), decreased appetite (21.2%) and constipation (20.2%). The most common grade 3 to 4 adverse reactions include: anaemia (12.9%), thrombocytopenia (7.9%), lymphopenia (7.8%) and fatigue (5.9%). Myelosuppression and renal toxicity occurred more frequently in participants who received ^{177}Lu vipivotide tetraxetan. The European Public Assessment Report notes the unfavourable safety profile of

^{177}Lu vipivotide tetraxetan plus SoC compared with SoC only. This is exemplified by higher numbers of all-causality and treatment-related adverse events (AEs), severe AEs, serious AEs and treatment-related deaths. The AEs of myelosuppression which are mostly treatment-related are the main causes of severe AEs, serious AEs, treatment-related deaths and tolerability issues. The Summary of Product Characteristics addresses the risk from radiation exposure to the individual patient and outlines radioprotection precautions that patients should follow to minimise radiation exposure to others.

3. Cost effectiveness of ^{177}Lu vipivotide tetraxetan

Comparisons of ^{177}Lu vipivotide tetraxetan to both SoC only and cabazitaxel were provided. Taxane-ineligible and taxane eligible populations were not considered separately in the cost-effectiveness model although these subpopulations have different comparators and likely differences in prognosis. The Applicant did not provide a comparison to Radium-223. The Review Group consider that this is a relevant comparator for the subpopulation of patients with symptomatic bone metastases and no extensive visceral metastases.

Methods

A partitioned survival model was submitted by the Applicant. The model included three mutually exclusive health states; Pre-Progression, Progressed Disease and Death. Key efficacy inputs were PFS and OS. Costs and outcomes were discounted at an annual rate of 4%. The analysis was conducted from the perspective of the HSE.

OS and PFS for ^{177}Lu vipivotide tetraxetan and SoC only were modelled by fitting parametric survival curves to individual patient data from the FAS of VISION. The use of the FAS, means that the proportion of missing data for the PFS outcome is high. To model OS and PFS for cabazitaxel, the Applicant applied HRs derived from the indirect comparisons described previously to the baseline hazard from the ^{177}Lu vipivotide tetraxetan arm. For OS, this HR was derived from the unanchored ITC while for PFS the corresponding HR was obtained from the Applicant's NMA.

Utility values were derived from EQ-5D-5L data collected in VISION which were mapped to EQ-5D-3L. The Applicant applied treatment-specific health state utility values to the ^{177}Lu vipivotide tetraxetan and SoC only arms in the model. In the cabazitaxel arm, the Applicant

applied the pre-progression utility from the SoC only arm in VISION and a progressed disease utility value, derived from a UK Early Access Programme. The Review Group had concerns as treatment-specific health state utilities from the open-label VISION trial, lack face validity and are likely associated with bias. The Review Group also considered the assumption of equivalence between the SoC only pre-progression utility and the cabazitaxel pre-progression utility to be inappropriate. Furthermore, the naïve indirect comparison of progressed disease utility between ^{177}Lu vipivotide tetraxetan (from VISION) and cabazitaxel (from an Early Access Programme) was not justified.

The Review Group addressed a number of limitations in the Applicant's cost-effectiveness analysis, through changes in the NCPE adjusted base case. These included both adjustment for missing data and alternative parametric model selection for OS and PFS as well as the assumption of ARPI usage in the ^{177}Lu vipivotide tetraxetan and SoC only arms of the model in line with VISION. The Review Group also used treatment-independent utilities from VISION in all treatment arms. An additional utility decrement was applied to the cabazitaxel arm in order to reflect the improved patient-reported outcomes in the ^{177}Lu vipivotide tetraxetan arm of TheraP and clinical opinion which suggests that ^{177}Lu vipivotide tetraxetan has a health-related quality of life benefit over cabazitaxel. However, the magnitude of this benefit remains highly uncertain.

Results

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 2.

Table 2: Applicant base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
^{177}Lu vipivotide tetraxetan	105,476	1.13	-	-	-
SoC only	21,425	1.10	84,231	0.42	202,452
Cabazitaxel	42,727	0.83	62,749	0.30	208,265

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care

[a] Corresponding probabilistic ICER using 5,000 iterations =€201,448/QALY (SoC comparison) and €209,888 (cabazitaxel comparison). Figures in the table are rounded, and so calculations may not be directly replicable

Results of the NCPE-adjusted base case are presented in Table 3. As noted previously, all available indirect comparisons of ^{177}Lu vipivotide tetraxetan versus cabazitaxel for the OS

outcome have substantial limitations and produced different effect estimates. Therefore, two scenarios are presented in the NCPE adjusted base case, one based on the unanchored ITC and the other on the NCPE alternative NMA.

Table 3: NCPE adjusted base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
^{177}Lu vipivotide tetraxetan	115,724	1.07	-	-	-
Standard of care	26,933	0.81	88,791	0.26	335,686
Cabazitaxel (unanchored ITC)	38,434	0.84	77,290	0.24	326,210
Cabazitaxel (NCPE alternative NMA)	38,766	1.02	76,959	0.06	1,338,064

ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison, NMA: network meta-analysis; QALY: quality-adjusted life year; SoC: standard of care

[a] Corresponding probabilistic ICER using 5,000 iterations =€336,547/QALY (SoC comparison), €334,808 (Cabazitaxel unanchored ITC comparison), €2,272,575 (Cabazitaxel NCPE alternative NMA). Figures in the table are rounded, and so calculations may not be directly replicable

In both the Applicant and NCPE adjusted base cases, the probability of cost-effectiveness for ^{177}Lu vipivotide tetraxetan versus both SoC only and cabazitaxel were 0% at both thresholds of €20,000 per QALY and €45,000 per QALY. Deterministic one-way sensitivity analysis indicated that the most influential parameters in the model for both the Applicant and the NCPE adjusted base case related to utilities.

An analysis of the price-ICER relationships was conducted for the NCPE adjusted base case. In the comparison of ^{177}Lu vipivotide tetraxetan to SoC, a discount of 94.7% is required to achieve cost effectiveness at a threshold of €45,000 per QALY. It is not possible to discount ^{177}Lu vipivotide tetraxetan sufficiently to reach the €20,000 per QALY threshold.

4. Budget impact of ^{177}Lu vipivotide tetraxetan

The price to wholesaler of one single dose vial of ^{177}Lu vipivotide tetraxetan (7,400 MBq) is €20,000. The total cost per patient per treatment course is €102,134 (€81,618 excluding VAT). This is based on the mean number of cycles (4.46) of ^{177}Lu vipivotide tetraxetan started per patient in VISION trial. The Applicant predicted that 15 patients will be treated with ^{177}Lu vipivotide tetraxetan in Year 1 rising to 84 patients in Year 5; total of 257 patients over five years. The five-year cumulative gross drug budget impact was an estimated €26.24 million (€20.97 million excluding VAT). The five-year cumulative net drug budget impact was

an estimated €25.74 million (€20.57 million excluding VAT).

5. Patient Organisation Submission

A patient organisation submission was received from Men Against Cancer (MAC).

6. Conclusion

The NCPE recommends that ^{177}Lu vipivotide tetraxetan (Pluvicto®) not be considered for reimbursement *.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.