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SMC2517

lutetium (^{177}Lu) vipivotide tetraxetan solution for injection or infusion (Pluvicto®)

Advanced Accelerator Applications

10 March 2023 *(Issued 08 September 2023)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

lutetium (^{177}Lu) vipivotide tetraxetan (Pluvicto®) is not recommended for use within NHSScotland.

Indication Under Review: Treatment of adult patients with prostate specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy or who are not medically suitable for taxanes.

^{177}Lu vipivotide tetraxetan, compared with cabazitaxel, increased prostate specific antigen (PSA) response rate in adults with mCRPC previously treated with docetaxel. The addition of ^{177}Lu vipivotide tetraxetan to standard of care increased progression free and overall survival in adults with mCRPC previously treated with at least one androgen receptor pathway inhibitor (ARPI) and one or two taxane regimens.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present sufficiently robust clinical and economic analyses to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

The radiopharmaceutical, ^{177}Lu vipivotide tetraxetan, comprises the radionuclide ^{177}Lu linked to a targeting moiety (vipivotide tetraxetan) that binds to PSMA, a transmembrane protein highly expressed in prostate cancer, including mCRPC. After binding to PSMA-expressing cancer cells, beta-minus emission from ^{177}Lu delivers radiation to the targeted and surrounding cells, thereby inducing DNA damage, which can lead to cell death. The recommended dose is 7,400MBq intravenously every six weeks (± one week) for a total of six doses. [1]

1.2. Disease background

Prostate cancer is initially treated with androgen deprivation therapy (ADT) either by chemical or surgical castration. After an initial response to ADT, patients with metastatic disease progress to a hormone insensitive stage, known as mCRPC, which is incurable and has a poor prognosis.[2] High expression of PSMA on prostate cancer cells is independently associated with reduced survival. Metastatic lesions are PSMA-positive in most patients with mCRPC.[3]

1.3. Treatment pathway and relevant comparators

The 2020 European Society for Medical Oncology (ESMO) guidelines on prostate cancer recommend an androgen receptor pathway inhibitor (ARPI), abiraterone or enzalutamide, for asymptomatic or mildly symptomatic patients with chemotherapy-naïve mCRPC. Olaparib can be considered after these new hormonal agents for patients with BRCA1 or BRCA2 mutations. Docetaxel is recommended for all patients with mCRPC. In the post-docetaxel setting, abiraterone, enzalutamide and cabazitaxel are options. However, the use of a second ARPI (abiraterone after enzalutamide or vice versa) is not recommended. Patients with bone metastases who are at risk for clinically significant skeletal related events can receive a bisphosphonate or denosumab. Radium-223 (^{223}Ra) dichloride is recommended for patients with bone-predominant, symptomatic mCRPC without visceral metastases but it is not recommended in combination with abiraterone and prednisolone.[4]

1.4. Category for decision-making process

On 5 April 2022, ^{177}Lu vipivotide tetraxetan received a positive scientific opinion under the Early Access to Medicines Scheme (EAMS) with the Medicines and Healthcare Products Regulatory Agency (MHRA). The indication was treatment of adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy or who are not medically suitable for taxanes.[5]

- Eligibility for a PACE meeting

^{177}Lu vipivotide tetraxetan meets SMC end of life and orphan equivalent criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

The main evidence of efficacy is from the TheraP and VISION studies.[3, 6] The submission also included observational data from a retrospective analysis of patients with mCRPC in England and a network meta-analysis (NMA) comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel.

Table 2.1. Overview of relevant studies

Criteria	TheraP[6, 7]	VISION[3]
Study Design	Australian, open-label, phase II study	International, open-label, phase III study
Eligible Patients	Adults with mCRPC previously treated with docetaxel who had progressive disease defined by increasing PSA per PCWG3 criteria and PSA ≥ 20 ng/mL. ECOG performance status 0 to 2. PSMA-positive on ^{68}Ga-PSMA-11 PET-CT with SUVmax ≥20 at disease site and >10 at all measurable metastatic sites; no discordant metastatic sites with ^{18}F-FDG-positive PET-CT and PSMA-negative (FDG intensity > ^{68}Ga-PSMA activity or ^{68}Ga-PSMA SUVmax <10).	Adults with mCRPC and disease progression after previous treatment with at least one ARPI and one or two taxane regimens. ECOG performance status 0 to 2. PSMA-positive on ^{68}Ga-PSMA-11 PET-CT scan (defined as at least one PSMA-positive metastatic lesion and no PSMA-negative lesions).
Treatments	• ^{177}Lu vipivotide tetraxetan IV every six weeks for a maximum of six cycles with initial dose of 8.5 GBq decreased by 0.5 GBq per cycle. • Cabazitaxel 20 mg/m^2 IV every three weeks for a maximum of ten doses. All received background ADT with LHRH analogue or surgical castration.	• ^{177}Lu vipivotide tetraxetan IV 7.4 GBq every six weeks for a maximum of six cycles plus SoC. • SoC, which excluded chemotherapy, radioisotopes and immunotherapy but could include hormonal therapy (e.g. ARPI), radiation, glucocorticoids, bisphosphonates, denosumab and others.
Randomisation	Randomisation was stratified by disease burden (>20 versus ≤20 sites on ^{68}Ga-PSMA PET-CT), prior enzalutamide or abiraterone (yes versus no) and study site. Patients equally assigned to ^{177}Lu vipivotide tetraxetan or cabazitaxel.	Randomisation was stratified by liver metastases (yes versus no), ECOG performance status (0 or 1 versus 2), LDH (≤260 IU/L versus >260 IU/L) and ARPI (yes versus no). Patients assigned in 2:1 ratio to ^{177}Lu vipivotide tetraxetan plus SoC or SoC.
Primary outcome	PSA response, defined as a reduction from baseline of at least 50% in PSA.	rPFS, defined as time to centrally reviewed disease progression on PCWG3 criteria or death from any cause. OS, defined as time to any cause death.
Secondary outcomes	PFS, defined as time to PSA progression (≥25% increase and ≥2 ng/mL after 12 weeks per PCWG3); radiographic progression on local CT and bone scans (per RECIST and PCWG3); initiation of non-protocol anticancer therapy or death from any cause. OS, defined as time to any cause death.	ORR on RECIST version 1.1 DCR on RECIST version 1.1 Time to SSE, defined as time from randomisation to first SSE or death from any cause.
Statistical analysis	p-values from analyses of secondary endpoints that were unadjusted for multiple comparisons were interpreted using Benjamini-Hochberg procedure.	The key secondary endpoints (ORR, DCR and time to SSE) were controlled for Type I error.

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; CT = computed tomography; DCR = disease control rate; ECOG = Eastern Co-operative Oncology Group; ^{18}F-FDG = 2-flourine-18 (^{18}F) fluoro-2-deoxy-D-glucose; ^{68}Ga-PSMA = gallium-68 (^{68}Ga)-prostate specific membrane antigen (PSMA)-11; GBq = gigabecquerel; IU/L – international units per litre; IV = intravenous; LDH = lactate dehydrogenase; LHRH = luteinising hormone releasing hormone; mCRPC = metastatic castration-resistant prostate cancer; ORR =overall response rate; OS = overall survival; PCWG3 = Prostate Cancer Working Group 3; PET-CT = positron-emission tomographic-computed tomography; PFS = progression free survival; PSA = prostate specific antigen; RECIST = response evaluation criteria in solid tumors; rPFA = radiographic progression free survival; SSE = symptomatic skeletal event; SoC = standard of care; SUVmax = maximum standardised uptake value.

In the TheraP study, all analyses were at data cut-off 20 July 2020 (triggered after 170 prostate specific antigen [PSA] progression free survival [PFS] events) when median follow-up was 18.4 months, except overall survival (OS). The final analysis of OS was at data cut-off 31 December 2021 when median follow-up was 36 months. The primary outcome, PSA response (≥50% reduction in PSA), was significantly increased with ^{177}Lu vipivotide tetraxetan compared with cabazitaxel in the intention-to-treat (ITT) population and within a sensitivity analysis of treated patients to account for high discontinuation rate prior to study treatment in the control group. Both PFS and OS exhibited non-proportional hazards. Benefits in PFS with ^{177}Lu vipivotide tetraxetan were not constant and were apparent after six months. Across both treatment groups, OS was similar. Results of pre-specified analysis including hazard ratio (HR) from Cox proportional hazards regression are detailed in Table 2.2 along with additional restricted mean survival time (RMST) analyses to account for non-proportional hazards.[6-8]

Table 2.2: Outcomes of TheraP study.[6-8]

	^{177}Lu vipivotide tetraxetan	**Cabazitaxel**	
PSA response rate			
Response in ITT	66% (65/99)	37% (37/101)	Difference 29% (95% CI: 16 to 42)*
Response in treated	66% (65/98)	44% (37/85)	Difference 23% (95% CI: 9 to 37)
Progression free survival (radiographic or PSA)			
Events	90	83	HR 0.63 (95% CI: 0.46 to 0.86)
Median, months	5.1	5.1	
RMST[a], months	7.1	5.0	
KM 12-month PFS	19%	3%	
Overall survival			
Deaths	77	70	HR 0.97 (95% CI: 0.7 to 1.4)
RMST[b], months	19.1	19.6	Difference -0.5 (95% CI: -3.7 to 2.7)
Objective response on RECIST 1.1[c]			
ORR, % (n/N)	49% (18/37)	24% (10/41)	RR 2.12 (95% CI: 1.1 to 4.08)

* primary outcome, p<0.001; (a) RMST = restricted mean survival time at 24 months; (b) RMST= restricted mean survival time at 36 months; (c) in 78 men with measurable disease by RECIST criteria at baseline; all responses were partial. CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; KM = Kaplan-Meier; ORR = objective response rate; PSA = prostate specific antigen; RECIST = response evaluation criteria in solid tumors; RR = relative risk.

In the VISION study, at the data cut-off for the final analysis (27 January 2021) median follow-up was 20.9 months. To address a high rate of discontinuation in the standard of care (SoC) arm prior to receiving study treatment, education measures were initiated on 5 March 2019 and analysis of radiographic PFS (rPFS) was modified to include only patients randomised after this date (385 and 196 patients in the ^{177}Lu vipivotide tetraxetan and SoC groups, respectively). OS was assessed in all randomised patients (551 and 280 patients in the respective groups). Key secondary outcomes

controlled for type 1 error, (objective response rate [ORR], disease control rate [DCR] and time to symptomatic skeletal event [SSE]), were analysed in those who had Response Evaluation Criteria in Solid Tumors (RECIST) evaluable disease and who were randomised after 5 March 2019. Both primary outcomes (OS and rPFS) and the key secondary outcomes (ORR, DCR and SSE) significantly improved with the addition of ^{177}Lu vipivotide tetraxetan to SoC as detailed in Table 2.3 below.[3]

Table 2.3: Outcomes of VISION Study.[3]

	^{177}Lu vipivotide tetraxetan	**Standard of Care**	
Overall survival			
Deaths (n/N)	343/551	187/280	HR 0.62 (95% CI: 0.52, 0.74)*
Median, months	15.3	11.3	
Radiographic progression free survival on PCWG3 by BICR			
Events (n/N)	254/385	93/196	HR 0.40 (95% CI: 0.29, 0.57)*
Median, months	8.7	3.4	
Time to first skeletal event			
Events (n/N)	256/385	137/196	HR 0.50 (95% CI: 0.40, 0.62)
Median, months	11.5	6.8	
Best overall response in patients with evaluable disease at baseline on RECIST by BICR			
Objective response rate (n/N)[a]	95/319	2/120	OR 24.99 (95% CI: 6.05, 103.24)
Disease control rate (n/N)[b]	284/319	80/120	OR 5.79 (95% CI: 3.18, 10.55)
Complete response, n	18	0	
Partial response, n	77	2	
Stable disease, n	68	30	

* primary outcome, p<0.001; (a) Objective response rate = complete or partial response on Response Evaluation Criteria in Solid Tumors (RECIST); (b) Disease control rate = complete or partial response, stable disease or non-complete response/non-progressive disease on Response Evaluation Criteria in Solid Tumors (RECIST); BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; OR = odds ratio; PCWG3 = Prostate Cancer Working Group 3;

2.2. Health-related quality of life outcomes

In TheraP, health-related quality of life was assessed on the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30). During the study, there appeared to be similar predicted mean scores across the treatment groups for EORTC QLQ-C30 global health status, functioning domains (physical, role, emotional and cognitive) and the following symptom domains: nausea and vomiting, pain, dyspnoea, insomnia, appetite loss and constipation. The mean social functioning score appears a little higher and mean diarrhoea and fatigue scores appear a little lower in the ^{177}Lu vipivotide tetraxetan group.[6]

In VISION, health-related quality of life was assessed on the Brief Pain Inventory Short Form (BPI-SF), Functional Assessment of Cancer Therapy - Prostate (FACT-P) and the EuroQoL-5 Dimension-5 Level (EQ-5D-5L) questionnaires.[3] Time to worsening FACT-P score (≥10 point decrease), clinical progression or death was delayed with the addition of ^{177}Lu vipivotide tetraxetan to SoC, with a HR of 0.54 (95% confidence interval [CI]: 0.45 to 0.66) and medians of 5.7 versus 2.2 months. Time to worsening of BPI-SF pain intensity (≥30% increase or ≥2 point increase), clinical progression or death was delayed with the addition of ^{177}Lu vipivotide tetraxetan to SoC,.[1, 3, 9]

2.3. Supportive studies

A retrospective, observational study of patients with mCRPC treated in English centres between January 2009 and December 2018 informed OS for cabazitaxel in the base case economic analysis, creating a naïve indirect comparison with the ^{177}Lu vipivotide tetraxetan arm of VISION. The submission focused on a group of patients who received cabazitaxel and had follow-up. Median OS in these patients was lower than that in the SoC group of VISION (11.3 months) suggesting differences across the populations. There was no supporting reference for these results.

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

A Bayesian NMA was presented to indirectly compare ^{177}Lu vipivotide tetraxetan with cabazitaxel and the HR from this was applied to the rPFS curve of ^{177}Lu vipivotide tetraxetan from VISION to estimate the cabazitaxel curve in the economic analysis using a method that assumes proportional hazards. The NMA is described in Table 2.4

Table 2.4: Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian network meta-analysis
Population	Adults with pre-treated progressive mCRPC in England
Comparators	^{177}Lu vipivotide tetraxetan was compared with cabazitaxel, olaparib, radium-223, ARPI and mitoxantrone-prednisolone
Studies included	8 studies
Outcomes	rPFS and OS
Results	Academic in confidence
Company conclusion	Academic in confidence

ARPI = androgen receptor pathway inhibitor; CI = confidence interval; HR = hazard ratio; mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; rPFS = radiographic progression free survival.

3. Summary of Safety Evidence

In the open-label TheraP study, adverse events reported at higher rates in the ^{177}Lu vipivotide tetraxetan group, compared with cabazitaxel, included dry mouth (60% versus 21%) and dry eyes (30% versus 3.5%). Renal and urinary adverse events were reported at lower rates in the ^{177}Lu vipivotide tetraxetan group, compared with cabazitaxel, 23% versus 46%, including lower rates of haematuria, 4.1% versus 20%. Other adverse events occurring at lower rates in the ^{177}Lu vipivotide tetraxetan group, compared with cabazitaxel, included diarrhoea (19% versus 56%), neuropathy (10% versus 27%), dysgeusia (12% versus 27%) and dizziness (4.1% versus 13%). Haematological adverse events were reported by 41% and 39% of patients in the respective groups, including anaemia (28% and 21%) and neutropenia (11% and 18%). There were also reductions in platelet count (30% and 4.7%) and white blood cells (11% and 7.1%). Other common adverse events included fatigue (76% and 75%), pain (72% and 66%), nausea (41% and 34%) and insomnia (9.0% and 15%).[6]

In the open-label VISION study, within the ^{177}Lu vipivotide tetraxetan plus SoC group, compared with SoC alone, there were higher rates of haematological adverse events including anaemia (32% versus 13%), thrombocytopenia (17% versus 4.4%), lymphopenia (14% versus 3.9%) and

leucopenia (12% versus 2.0%). There were also higher rates of gastrointestinal adverse events including nausea (35% versus 17%), vomiting (19% versus 6.3%), constipation (20% versus 11%) and diarrhoea (19% versus 2.9%) and other adverse events such as fatigue (43% versus 23%), dry mouth (39% versus 0.5%), arthralgia (22% versus 13%) and decreased appetite (21% versus 15%).[3]

The summary of product characteristics (SPC) provides guidance on minimising risks of radiation exposure to the patient and their family. ^{177}Lu vipivotide tetraxetan contributes to a patient's overall long-term cumulative radiation exposure, which is associated with an increased risk for cancer.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the TheraP study, ^{177}Lu vipivotide tetraxetan compared with cabazitaxel significantly increased PSA response rate by 29% in the ITT population and 23% in those who received treatment. It was associated with improved PFS, with non-proportional hazards. That is, the difference in risk of progression or death was observed at the later stages of follow-up. In the final analysis of OS, there was no difference between the treatment groups.[6-8]
- In the VISION study, addition of ^{177}Lu vipivotide tetraxetan to SoC significantly increased rPFS, OS, ORR and DCR.[3]

4.2. Key uncertainties

- TheraP was primarily designed to assess PSA response rate. However, it was estimated to have a least 80% power to detect HR of 0.65 after 170 events for PFS and 170 deaths for OS. The analysis of PFS at data cut-off 20 July 2020 was triggered after 170 PFS occurred. At the final analysis of OS (data cut-off 31 December 2021) 147 deaths had occurred and the study may have had less than 80% power to detect a difference in OS. Visual inspection of the Kaplan-Meier OS curves indicates that these are similar with no suggestion of a difference between groups.[6-8]
- PFS data input to economic analyses do not capture the non-proportional hazard relationship between ^{177}Lu vipivotide tetraxetan and cabazitaxel observed in the TheraP study.[6-8] In the base case economic analysis, the HR from the indirect comparison is applied to the rPFS survival curve of ^{177}Lu vipivotide tetraxetan from VISION to estimate the cabazitaxel curve. Although this HR is similar to that from TheraP, application in a proportional manner may underestimate the effect of cabazitaxel during the initial months of treatment.
- The NMA indirectly comparing ^{177}Lu vipivotide tetraxetan with cabazitaxel, which provided rPFS data for the economic analysis has a number of limitations. It excluded the direct comparison, TheraP, but included several irrelevant studies and interventions. In the network ^{177}Lu vipivotide tetraxetan and cabazitaxel were linked via the VISION study[3] (^{177}Lu vipivotide tetraxetan plus SoC versus SoC in the subgroup that had an ARPI) and the CARD study[10] (APRI versus cabazitaxel plus prednisolone). Data for VISION were from a post hoc subgroup analysis. There was heterogeneity between studies in design, length of follow-up

and patient population, including differences in prior treatments and testing for PSMA-positive disease, which was part of the VISION study only. Given the limitations, the results should be interpreted with caution.

- OS data input to economic analyses do not correspond with results of TheraP, which suggest no difference in OS between ^{177}Lu vipivotide tetraxetan with cabazitaxel.[6-8] In the base case economic analysis, OS for ^{177}Lu vipivotide tetraxetan is derived from the treatment arm of the VISION study[3] and OS for cabazitaxel is derived from an observational, retrospective analysis of patients treated within the UK. A reference for the study results was not provided. Comparison of these differing populations is subject to bias and provides an advantage in OS for ^{177}Lu vipivotide tetraxetan that was not observed in the direct comparison, TheraP.[6, 7] Also, median OS was longer in the SoC arm in VISION[3] than with cabazitaxel in the observational analysis, which increases uncertainty about the validity of the results.
- The observational analysis included data from 2009 and 2018 with a focus on the group who received cabazitaxel, which was licensed in April 2011 for its sole indication (mCRPC after docetaxel)[11] and recommended by the National Institute of Health and Care Excellence (NICE) in May 2016 (TA391).[12] In this observational analysis, the majority of patients commenced cabazitaxel after 2015. The analysis of OS did not include patients who did not have any follow-up data at the cut-off and censored patients who were still alive. Just over half of patients in the cabazitaxel group were reported to have previously had both an ARPI and docetaxel and additional analysis in this group was provided, with data censored for patients who were alive at the cut-off (company response 23.11.22). In 2016, NICE published technology appraisals (TA377 and TA378) which recommended enzalutamide and abiraterone for use pre-docetaxel when they had previously been indicated post-docetaxel.[13, 14] The impact of the changing treatment pathway on patients in the observational analysis is unclear.
- In VISION, 68% (139/205) of patients in the SoC arm received an ARPI during the study.[3] EMSO guidelines do not recommend the use of a second ARPI.[4] This SoC arm in VISION may not reflect current practice where cabazitaxel is offered to patients who have had an ARPI and docetaxel. There was no evidence comparing ^{177}Lu vipivotide tetraxetan with ^{223}Ra dichloride, which may be offered at this stage of the disease to patients with bone metastases only.
- Both TheraP and VISION were open-label and this may impact disposition and study results, especially at later points in survival analysis. In TheraP, more patients withdrew prior to receiving study treatment in the cabazitaxel group, compared with ^{177}Lu vipivotide tetraxetan, 16% (16/101) versus 1% (1/99), which is likely to introduce bias. Rates of early discontinuation of treatment due to patient or physician decision were higher in the cabazitaxel group: 38% versus 13% of ITT (45% versus 13% of treated patients), respectively.[6] There were larger discontinuation rates in VISION, where more patients did not receive study treatment with SoC alone versus ^{177}Lu vipivotide tetraxetan, 28% (79/280) versus 4.0% (22/551) in ITT, and in population enrolled after educational measures on 5 March 2019, 16% (32/196) versus 4.2% (16/385). Rates of early

discontinuation due to patient or physician decision were higher in the SoC arm, 16% versus 7.1% in ITT (22% versus 7.4% of treated patients). [3, 9]

- In TheraP, there was crossover of patients in both groups after discontinuing study treatment. At the final analysis of OS (31 December 2021), in the ^{177}Lu vipivotide tetraxetan group, subsequent treatment included additional ^{177}Lu vipivotide tetraxetan for 5 patients and cabazitaxel for 32 patients. In the cabazitaxel group, subsequent treatment included cabazitaxel for 21 patients and ^{177}Lu vipivotide tetraxetan for 20 patients. This may limit OS data.[7]
- In TheraP, the dose of ^{177}Lu vipivotide tetraxetan (8.5 GBq reducing by 0.5 GBq every cycle for up to six cycles) was different from the licensed dose (7.5 GBq every cycle for up to six cycles).[1, 6]
- TheraP did not require patients to have previously received treatment with an ARPI but 91% (182/200) had previously had these and, therefore, were representative of the indication for use in adults with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy.[1, 6] All of the patients in VISION had received at least one ARPI and one or two taxane regimens. ^{177}Lu vipivotide tetraxetan is also licensed for use in patients who are medically unsuitable for taxanes. The VISION study recruited patients who has received one prior taxane if they were not willing to receive a second taxane or their physician deems then unsuitable for another taxane and these comprised about 58% of the study population. The OS and rPFS HR (0.59 and 0.39) in this subgroup appear consistent with the overall population. However, there is no evidence in patients who are not medically suitable for a first taxane regimen.
- In VISION, patients were required to have a positive ^{68}Ga-PSMA-11 PET-CT scan. TheraP had more stringent molecular imaging criteria based on both ^{18}F-FDG and ^{68}Ga-PSMA PET-CT scans, which resulted in 28% of screened patients being excluded from the study due to discordance between these. The marketing authorisation does not specify specific PSMA imaging criteria.[1] The TheraP population may represent a subgroup of those who could be treated in practice.[1, 3, 6]
- The open-label design of TheraP and VISION may limit the assessment of subjective outcomes such as safety and quality of life.

4.3. MHRA/EMA specific obligations

There are no ongoing studies to address the key uncertainties in the clinical evidence presented.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that there is an unmet need for effective therapies in the treatment of mCRPC post ARPI and docetaxel. They noted that ^{177}Lu vipivotide tetraxetan is a therapeutic advance is this setting as it provides an alternative to the limited available options. They note that it would be used in place of cabazitaxel or, in patients with bone-only metastases (without visceral metastases), it may displace ^{223}Ra dichloride.

4.5. Service implications

Clinical experts consulted by SMC considered that the introduction of ^{177}Lu vipivotide tetraxetan may impact service delivery through requirements for the development of additional capacity in specialist services that can deliver radiopharmaceuticals. They also noted a potential increased capacity to screen patients for PSMA.

Companion diagnostic required: contact local laboratory for information.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of lutetium (^{177}Lu) vipivotide tetraxetan, as an orphan equivalent and end-of-life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Prostate cancer is the most common cancer in men in Scotland, accounting for a quarter of all cancers. Metastatic castration-resistant prostate cancer (mCRPC) is an incurable illness which is associated with significant morbidity and impacts the physical and mental well-being of patients.
- Following treatment with androgen receptor pathway inhibitor (ARPI) and taxane chemotherapy, there are limited further treatment options and these are only suitable for a minority of patients. They include radium-223 for those with bone metastases, chemotherapy for those who are sufficiently fit and olaparib for the small subset of patients with a germline/somatic BRCA mutation. There remains a high unmet need for further effective treatment options for patients with visceral metastases and those not fit enough to receive chemotherapy.
- Lutetium (^{177}Lu) vipivotide tetraxetan would provide a further novel targeted treatment suitable for patients with visceral and bone metastases and for those not fit enough to receive further chemotherapy. The availability of a further treatment may relieve the psychological distress for patients and their families of exhausting treatment options.
- Lutetium (^{177}Lu) vipivotide tetraxetan may control disease symptoms, delay time to disease progression, maintain quality of life and improve survival. This may relieve the burden of disease on patients and family and carers allowing them to lead a more normal life.
- Lutetium (^{177}Lu) vipivotide tetraxetan is well-tolerated with a manageable side effect profile compared with chemotherapy allowing patients to maintain their quality of life. It has the advantage over radium-223 of having efficacy on visceral as well as bone metastases.
- Significant service implications would be required to deliver lutetium (^{177}Lu) vipivotide tetraxetan. Routine PSMA PET-scanning would be needed to identify eligible patients. Sufficient trained staff and increased specific bed/chair capacity would be needed to administer this radiopharmaceutical.

Additional Patient and Carer Involvement

We received patient group submissions from Prostate Cancer UK, Prostate Scotland and Tackle Prostate Cancer. All three organisations are registered charities. Prostate Cancer UK has received less than 1% pharmaceutical company funding in the past two years, including from the submitting company. Prostate Scotland has not received any pharmaceutical company funding in the past two years. Tackle Prostate Cancer has received 18% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from all three organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (10 years)
Population	The analysis covered ^{177}Lu vipivotide tetraxetan use in the full licensed indication.
Comparators	Cabazitaxel and standard of care (SoC)
Model description	Partitioned survival model with three health states; progression-free, progressed and dead.
Clinical data	rPFS, OS, time to first SSE and safety data for the comparison of ^{177}Lu vipivotide tetraxetan and SoC were obtained from the VISION study. For the comparison with cabazitaxel, comparator data came from various sources. rPFS was modelled using the inverse HR for cabazitaxel from the company-provided NMA and applying it to data from the VISION study for ^{177}Lu vipivotide tetraxetan. UK-specific real world evidence was used for the modelling of OS. Data on SSEs and safety came from the CARD study.
Extrapolation	Long-term rPFS and OS from VISION were modelled using the 2-knot stratified flexible Weibull statistical model. The log-normal was used for the extrapolation of time to first SSE. For cabazitaxel, OS observational data covered the full time horizon of the model and as such no extrapolation was needed.
Quality of life	Treatment and health state-specific utility weights were derived using EQ-5D-5L data from VISION, mapped to 3L using a published algorithm. For cabazitaxel, the rPFS utility weight was assumed equal to that for SoC from VISION. The post-progression utility weight (0.627) was obtained from NICE TA391. No utility decrements associated with adverse events or SSEs were applied in the base case analysis.
Costs and resource use	Apart from medicine acquisition and administration costs for ^{177}Lu vipivotide tetraxetan, SoC and cabazitaxel , other costs included in the analysis were those associated with disease monitoring (consultant and nurse appointments, CT scans, blood tests, MRIs, ECGs, etc), treatment of adverse events and symptomatic skeletal events, subsequent treatments, and concomitant treatments (in scenario analysis only).
PAS	A PAS was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under

	the PAS, a discount was offered on the list price. A PAS discount is also in place for cabazitaxel.

6.2. Results

The results presented include the PAS for ^{177}Lu vipivotide tetraxetan but do not take account of the PAS for cabazitaxel due to commercial confidentiality and competition law issues. Both discounts were considered in the results used for decision-making.

Base case results as pairwise comparisons are presented in table 6.2 below. The quality-adjusted life-year (QALY) gain is primarily driven by a modelled improvement in rPFS, which is associated with higher utility weight for ^{177}Lu vipivotide tetraxetan, but also by a longer stay in the post-progression state due to improved survival. The cost differences between ^{177}Lu vipivotide tetraxetan and comparators is primarily driven by medicine acquisition costs.

Table 6.2: Base case results (PAS for ^{177}Lu vipivotide tetraxetan, list price for cabazitaxel)

Intervention	ICER inc. (£/QALY)
^{177}Lu vipivotide tetraxetan	-
Cabazitaxel	25,726
SOC	108,377
Abbreviations: ICER, incremental life-year: QALYs, quality-adjusted life years; SOC, standard of care.	

6.3. Sensitivity analyses

A number of sensitivity analyses were provided by the company with the main scenarios additionally requested by SMC. Key scenarios are summarised in Table 6.3.

Table 6.3: Selected scenario analyses (PAS for ^{177}Lu vipivotide tetraxetan, list price for cabazitaxel**)**

	Scenario	Base case	ICER vs Cabazitaxel (£/QALY)	ICER vs SOC (£/QALY)
0	Base case	-	25,726	108,377
1	Using the inverse of HR from a revised RE NMA excluding TheraP study for the modelling of rPFS for cabazitaxel	Using the inverse of HR from FE NMA excluding TheraP study	25,774	NA
2	TheraP study directly used for the modelling of rPFS for both Lu vipivotide tetraxetan and cabazitaxel	Using the inverse of HR from FE NMA excluding TheraP study	Not provided	NA
3.	Applying a treatment waning effect to rPFS for ^{177}Lu vipivotide tetraxetan from year 2 until year 4, where HR=1	No treatment waning	25,855	108,944
4	Using the inverse of HR from the initially provided RE NMA for the modelling of OS for cabazitaxel	UK-specific real world evidence for cabazitaxel OS	39,098	NA
5	HR for OS derived using random effects in the revised NMA,	UK-specific real world evidence for cabazitaxel OS	Not provided	NA

	(including the TheraP study) in the comparison with cabazitaxel.			
6	Using the inverse of HR from the initially provided RE NMA for the modelling of OS for cabazitaxel and applying a treatment waning effect from year 2 until year 4, where HR =1	UK-specific real world evidence for cabazitaxel OS; No treatment waning effect for ^{177}Lu vipivotide tetraxetan OS	42,594	119,409
7	No difference in survival between ^{177}Lu vipivotide tetraxetan and cabazitaxel is assumed (HR=1)	OS data from VISION for ^{177}Lu vipivotide tetraxetan and UK-specific real world evidence for cabazitaxel OS	Not provided	NA
8	OS and rPFS are based on the data from TheraP study for ^{177}Lu vipivotide tetraxetan and cabazitaxel	Inverse of HR from NMA (excluding TheraP study) applied to data from VISION OS data from VISION for ^{177}Lu vipivotide tetraxetan and UK-specific real world evidence for cabazitaxel OS	Not provided	NA
9	Treatment-independent health state utility weights + utility decrements associated with AE and SSE.	Treatment-specific and health state specific utility weights	31,160	121,829
10	Excluding the cost of concomitant medication in the cabazitaxel arm	Assuming the overall distribution of concomitant medication in VISION for cabazitaxel	41,069	NA
11	Combined scenarios 6 and 9		62,867	135,650
12	Combined scenarios 1, 3, 6 and 9		64,046	136,171
Abbreviations: SOC, standard of care; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; FE, fixed effects; RE, random effects; HR, hazards ratio; OS, overall survival; rPFS, radiographic progression-free survival; AE, adverse events; SSE, symptomatic skeletal events;				

6.4. Key strengths

Key strengths of the analysis include the use of an appropriate model structure, time horizon, availability and use of a phase III RCT clinical efficacy, safety and health-related-quality of life data and the use of overall appropriate costs in the analysis.

6.5. Key uncertainties

The analysis is associated with the following uncertainties:

- Modelling of rPFS in the comparator arm (cabazitaxel) - The company applies a HR to the K-M curve for ^{177}Lu vipivotide tetraxetan from VISION, failing to use rPFS data from the phase II TheraP study, which directly compares the two treatments showing non-proportional hazards

and a smaller treatment effect for ^{177}Lu vipivotide tetraxetan. Despite the limitations of the TheraP study, the company's approach is likely underestimating the efficacy of cabazitaxel as the economic model predicts lower long term efficacy than that of SoC. Scenario analyses 1 and 3 explore the effect of using a revised HR and implementing a treatment waning effect and show minimal impact on the ICER. However, scenario 2 where data from the TheraP study are used directly has not been provided.

- Modelling of OS in the comparator arm (cabazitaxel) – The company used UK-based observational data in a naïve comparison with trial data for ^{177}Lu vipivotide tetraxetan from VISION. This approach showed clinically implausible results of cabazitaxel having worse survival than SoC. It is likely that the company's base case approach to modelling survival benefit vs cabazitaxel overestimates the efficacy of ^{177}Lu vipivotide tetraxetan in clinical practice. Scenario 4, where a constant survival benefit was assumed for ^{177}Lu vipivotide tetraxetan vs cabazitaxel as shown in the company-provided random effects NMA, shows an increase in the ICER. NMA results incorporating the TheraP study were not provided (scenario 5). Incorporating a treatment waning effect also leads to an increase in the ICER (scenario 6). Direct comparative OS data are available from the phase II TheraP study, showing no survival benefit for ^{177}Lu vipivotide tetraxetan. Scenarios 7 and 8, where rPFS and OS assumptions in line with these results are made, were also not provided.
- No available clinical and cost-effectiveness evidence for patients who are medically unsuitable for any taxanes (second line ^{177}Lu vipivotide tetraxetan) with the company assuming the results from the VISION study can generalise to this population. SMC clinical expert responses indicate this assumption may be reasonable, although it remains a source of uncertainty.
- No cost-effectiveness evidence versus other relevant comparators such as ^{223}Ra dichloride, for patients with bone metastasis and no visceral metastasis and olaparib for patients with BRCA mutations. The Committee considered that on balance, these groups were relatively small and as such, cabazitaxel and SoC were the relevant comparators for the majority of patients.
- Using treatment-dependent health state utility weights and assuming the progression-free health state utility weight for cabazitaxel equals that of standard of care from VISION, potentially underestimating the HRQoL for cabazitaxel. A preferred approach is the use of treatment-independent health state utilities and applying utility decrements associated with adverse events and SSEs. Using treatment-independent utility weights and applying utility decrements associated with adverse events and SSE leads to an increase in the ICER (scenario 9).
- Using a potentially inappropriate source of safety data for cabazitaxel, which overestimates the costs of treatment and the utility decrements associated with adverse events for cabazitaxel (used only in scenario analysis). Direct comparative safety data are available (TheraP study) but have not been utilized.

7. Conclusion

The Committee considered the benefits of ^{177}Lu vipivotide tetraxetan in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as ^{177}Lu vipivotide tetraxetan is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept ^{177}Lu vipivotide tetraxetan for use in NHSScotland.

8. Guidelines and Protocols

The National Institute for Health and Clinical Excellence (NICE) NICE guideline 131 (NG131) 'Prostate cancer: diagnosis and management' was published in May 2019. See here.

The European Society of Medical Oncology (ESMO) guideline 'Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up' was published in 2020. See here.

9. Additional Information

9.1. Product availability date

01 July 2023

9.2. Summary of product characteristics

See SPC for further information including dosing and safety. ^{177}Lu vipivotide tetraxetan 1,000 MBq/mL solution for injection or infusion (Pluvicto®) SPC.

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per course (£)
^{177}Lu vipivotide tetraxetan	7,400 MBq intravenously every 6 weeks for up to 6 doses	120,000

Costs from new product assessment form (NPAF). Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 246 patients eligible for treatment with lutetium (^{177}Lu) vipivotide tetraxetan each year, to which confidential uptake rates were applied.

SMC is unable to publish the budget impact due to commercial in confidence issues.

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This assessment is based on data submitted by the applicant company up to and including 13 January 2023.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.