CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

lutetium (^{177}Lu) vipivotide tetraxetan (Pluvicto)

Indication: Treatment of adults with prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer who have received at least one androgen receptor pathway inhibitor and taxane-based chemotherapy.

Sponsor: Advanced Accelerator Applications Canada, Inc.

Recommendation: Reimburse with Conditions

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Single Technology

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Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that lutetium [^{177}Lu] vipivotide tetraxetan be reimbursed for the treatment of adults with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have received at least one androgen receptor pathway inhibitor (ARPI) and at least one taxane-based chemotherapy, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase 3 randomized controlled trial (RCT) (VISION; N = 831) demonstrated that treatment with ^{177}Lu vipivotide tetraxetan in combination with best supportive care (BSC) or best standard of care (BSoC) resulted in a clinically meaningful improvement in overall survival (OS) compared with BSC/BSoC alone in patients with progressive PSMA-positive mCRPC who had previously received at least one ARPI and at least one taxane regimen (hazard ratio [HR] = 0.62; 95% CI, 0.52 to 0.74; $p < 0.001$). The VISION trial excluded patients who were considered eligible to receive cabazitaxel as a second taxane regimen; however, one phase 2 study (TheraP; N = 200) enrolled patients for whom cabazitaxel was considered the appropriate treatment option. In the TheraP trial, ^{177}Lu vipivotide tetraxetan was statistically superior to cabazitaxel for the primary endpoint of prostate specific antigen (PSA) response, progression-free survival (PFS), radiographic progression free survival (rPFS), objective response rate (ORR), and pain progression-free survival. TheraP was not designed or powered to evaluate potential differences in OS.

There are currently limited effective treatments for patients with mCRPC who have progressed following treatment with an ARPI and docetaxel and all stakeholders identified important patient unmet medical needs, particularly for patients who may be ineligible to receive cabazitaxel. pERC concluded that ^{177}Lu vipivotide tetraxetan may help address identified patient needs for an additional effective treatment option that may prolong survival and delay the onset or worsening of symptoms for those living with mCRPC.

Based on the limitations with comparative evidence for ^{177}Lu vipivotide tetraxetan and cabazitaxel, pERC could not derive conclusions regarding the relative effectiveness and cost-effectiveness of ^{177}Lu vipivotide tetraxetan and cabazitaxel. Using the sponsor submitted price for ^{177}Lu vipivotide tetraxetan and publicly listed prices for all other drug costs, when compared with BSC/BSoC (i.e., excluding cabazitaxel from consideration), the incremental cost-effectiveness ratio (ICER) for ^{177}Lu vipivotide tetraxetan was $451,407 per QALY gained. At this ICER, ^{177}Lu vipivotide tetraxetan is not cost-effective at a $50,000 per QALY gained willingness to pay (WTP) threshold for patients with prostate-specific membrane antigen positron emission tomography-scan positive mCRPC who have received androgen receptor pathway inhibitor and taxane-based chemotherapy.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason	Implementation Guidance
Initiation		
1. Treatment with ^{177}Lu vipivotide tetraxetan should only be initiated in patients with mCRPC who are 1.1. PSMA positive as per the criteria used in VISION.	The Health Canada approved indication is restricted to patients who have PSMA positive mCRPC.	In the VISION trial, PSMA positive patients were identified using ^{68}Ga-PSMA-11 PET-CT scans based on the following criteria: 1. At least one ^{68}Ga-PSMA-11 positive lesion. A PET-CT positive lesion was defined as having uptake greater than normal liver parenchyma, whereas a negative lesion were those tumours with uptake less than or equal to liver uptake. 2. All lymph nodes that measured ≥ 2.5 cm in short axis had to be ^{68}Ga-PSMA-11 positive. 3. All bone metastases with soft tissue component ≥ 1.0 cm in short axis had to be ^{68}Ga-PSMA-11 positive (bone metastases without a soft tissue component or with a soft tissue component of less than 1.0 cm were not considered for PSMA assessment in screening). 4. All solid organ metastases ≥ 1.0 cm in short axis had to be ^{68}Ga-PSMA-11 positive. Patients must have at least one PSMA-positive lesion identified on PSMA-PET (i.e., criterion 1) and no negative lesions (i.e., criteria 2 to 4) to be eligible.
1.2. Previously treated an APRI and at least one prior taxane-containing regimen.	The Health Canada approved indication is restricted to patients who have received at least 1 ARPI and at least 1 taxane-based chemotherapy.	—
1.3. Good performance status.	The VISION trial included patients with ECOG performance status of 0, 1, or 2.	—
Discontinuation		
2. Treatment with ^{177}Lu vipivotide tetraxetan should be discontinued upon the occurrence of any of the following:	The product monograph recommends discontinuation upon disease progression or unacceptable toxicity. ^{177}Lu vipivotide tetraxetan can be associated with serious	Patients should be evaluated with clinical examination and laboratory evaluations prior to every cycle of ^{177}Lu vipivotide tetraxetan.

Reimbursement Condition	Reason	Implementation Guidance
2.1. Disease progression based on clinical, PSA, and radiographic factors. 2.2. Unacceptable toxicity.	adverse events, including myelosuppression and renal toxicity.	
3. Assessment for disease progression should be based on clinical and radiographic evaluations every 3 months, or as per physician's discretion.	The VISION trial included imaging at baseline, then every 8 weeks for 24 weeks, then every 12 weeks until end of treatment. According to clinical expert input, imaging for patients with mCRPC would be performed once every 12 weeks in practice or earlier in response to changes in symptoms and/or clinical examination.	—
Prescribing		
4. ^{177}Lu vipivotide tetraxetan should be prescribed by an oncologist with expertise in the management of prostate cancer.	To ensure that ^{177}Lu vipivotide tetraxetan is prescribed only for appropriate patients, and that adverse effects are managed appropriately.	—
5. ^{177}Lu vipivotide tetraxetan should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals	As per recommendations in the Health Canada approved product monograph.	Patients may be required to travel to access radiopharmaceutical facilities.
6. ^{177}Lu vipivotide tetraxetan should not be prescribed in combination with anticancer therapies other than ADT.	pERC and the clinical experts consulted by CADTH noted the potential benefit of any combination usage of ^{177}Lu vipivotide tetraxetan with other anticancer therapies is highly uncertain.	—
7. Reimbursement should be limited to a maximum of 6 cycles.	Health Canada approved product monograph recommends a maximum of 6 doses.	—
Pricing		
8. A reduction in price.	The ICER for ^{177}Lu vipivotide tetraxetan is $451,407 per QALY gained when compared with BSC/BSoC. A price reduction of 92% would be required for ^{177}Lu vipivotide tetraxetan to be able to achieve an ICER of $50,000 per QALY gained compared to BSC/BSoC.	—

Reimbursement Condition	Reason	Implementation Guidance
Feasibility of Adoption		
9. The feasibility of adoption of ^{177}Lu vipivotide tetraxetan must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—
10. Organizational feasibility must be addressed so that jurisdictions have the infrastructure in place to implement treatment with ^{177}Lu vipivotide tetraxetan: 10.1. Access to specialized facilities that can administer radiopharmaceuticals.	Administration of ^{177}Lu vipivotide tetraxetan, a radiopharmaceutical, is resource intensive due to its limited shelf life and complex preparation and administration. There are a limited number of specialized centers in Canada that have the infrastructure in place to prepare, administer, and dispose ^{177}Lu vipivotide tetraxetan in a safe manner.	Product monograph states that ^{177}Lu vipivotide tetraxetan should be used by or under the control of healthcare providers who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.
10.2. Access to PSMA PET-CT diagnostic testing.	Identification of patients with PSMA positive mCRPC requires diagnosis with PET-CT imaging.	PET-CT capacity and nuclear medicine treatment facilities would need to be increased to accommodate PSMA testing and the delivery of ^{177}Lu vipivotide tetraxetan.

ARPI = androgen receptor pathway inhibitor; BSC = best supportive care; BSoC = best standard of care; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; mCRPC = metastatic castration-resistant prostate cancer; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; SOC = standard of care.

Discussion Points

- **Place in therapy:** pERC discussed the 3 relevant subpopulations for consideration in this review:
  - **Patients previously treated with ARPI, docetaxel, and cabazitaxel:** In the VISION trial, 41.2% of the trial population had received 2 prior taxane-containing regimens at the time of enrolment. The subgroup analysis of OS based on the number of prior taxane regimens favoured ^{177}Lu vipivotide tetraxetan versus BSC/BSoC alone for those who had received 2 or more prior taxane regimens (HR: 0.73; 95% CI, 0.53 to 0.99). pERC noted that ^{177}Lu vipivotide tetraxetan could contribute to filling an unmet need in this population, where no standard therapies have been shown to meaningfully improve OS.
  - **Patients previously treated with ARPI and docetaxel who are ineligible to receive cabazitaxel**: The inclusion criteria for the phase 3 VISION trial limited enrollment to patients who had received prior therapy with at least one taxane regimen (57.9% had received 1 taxane-containing regimen) and, for those with exposure to only a single taxane regimen, they must have been deemed unsuitable to receive a second taxane regimen (e.g., frailty assessed by geriatric or health status evaluation or intolerance). pERC noted that the subgroup analysis based on the number of prior taxane regimen favoured ^{177}Lu vipivotide tetraxetan versus BSC/BSoC alone for those who had received a single prior taxane regimen (HR: 0.59; 95% CI, 0.46 to 0.75). pERC noted that ^{177}Lu vipivotide tetraxetan could contribute to filling an unmet need in this population, where no standard therapies have been shown to meaningfully improve OS.
  - **Patients previously treated with ARPI and docetaxel who are eligible to receive cabazitaxel:** The inclusion criteria VISION trial specified that patients who were previously treated with docetaxel and considered eligible to receive

cabazitaxel were to be excluded from VISION. As this population is included in the Health Canada approved indication, CADTH considered this to be an important gap in the evidence and therefore, summarized the phase 2 TheraP trial, which enrolled patients with prior exposure to docetaxel and for whom cabazitaxel was considered the appropriate treatment option. Although not designed or powered to evaluate differences in OS, pERC considered the TheraP trial and noted that results provided some evidence of comparative efficacy for ^{177}Lu vipivotide tetraxetan versus cabazitaxel.

- **Patient needs:** Patient and clinician input to CADTH identified an unmet need in the treatment of adults with mCRPC who have demonstrated disease progression on an ARPI and docetaxel. The committee concluded that ^{177}Lu vipivotide tetraxetan could provide an additional treatment option for these patients, particularly those who are ineligible for treatment with cabazitaxel or have demonstrated disease progression following treatment with cabazitaxel.

- **Quality of life:** Patients living with mCRPC have expressed a need for new effective treatments that can help maintain their quality of life. In the VISION trial, ^{177}Lu vipivotide tetraxetan + BSC/BSoC demonstrated improvements in time to worsening relative to baseline in Functional Assessment of Cancer Therapy – Prostate (FACT-P), Functional Assessment of Cancer Therapy – General (FACT-G), FACT – Prostate Advanced Prostate-8 (FAPSI-8), and EQ-5D-5L compared with BSC/BSoC. pERC acknowledged these favourable results for quality-of-life endpoints but noted that there are important limitations with the statistical analysis of these endpoints due to the high rate of early withdrawal rate from the control group and that the analyses were not considered reliable by CADTH or regulatory authorities due to the probability of bias.

- **Access challenges to *PSMA* testing:** pERC noted that PSMA testing via PET-CT is not widely available in Canadian practice, both due to an under-supply of PSMA PET-CT scans, as well as the infrastructure (including radiotracers, machinery, personnel, physical spaces) needed to support use. A CADTH analysis estimated that the diagnostic use of PSMA PET-CT would require a substantial increase (approximately 25%) in the existing PET-CT exam volume in Canada. Given these supply and infrastructure limitations, it is unlikely that all patients with mCRPC who are candidates for ^{177}Lu vipivotide tetraxetan would be able to receive a PSMA PET-CT exam in a reasonable timeframe. This raises access and distributive justice challenges about how limited access to testing would be allocated, and a need to increase the supply of PSMA PET-CT equitably across Canadian provinces to enable access to this test and ultimately to ^{177}Lu vipivotide tetraxetan. This calls for clarity, transparency, and appropriate stakeholder engagement for policy decisions about expanding PET-CT capacity in the context of considering responsible use of resources and the long-term sustainability of the Canadian healthcare system, and to prevent further disadvantaging or entrenching disparities in health outcomes for certain groups.

- **Access challenges to ^{177}Lu vipivotide tetraxetan as a radiopharmaceutical:** pERC discussed additional challenges in equity of access to 177Lu vipivotide tetraxetan given the difficulties in manufacturing, transporting, delivering, and disposal, and how delays in access could prevent patients who are often near the end of their lives from obtaining this therapy. Infrastructural requirements for delivery would require specialized personnel and facilities, limiting access to specialized treatment centres. There is a need to ensure safe and efficient manufacturing and delivery of this therapy, and to develop processes or supports to ensure equitable access based on medical need.

- **Equity in the management of radiation exposure:** The radioactivity of patients following the administration of 177Lu vipivotide tetraxetan requires a modification of activities and proximity to household members. These adaptations may pose challenges for some individuals or groups (e.g., those who are living in congregate settings or those without readily accessible laundry facilities). These risks may disproportionately affect lower socioeconomic groups and they may consequently have less access to this therapy.

- **Indirect comparison:** In the absence of adequately powered direct comparisons of ^{177}Lu vipivotide tetraxetan versus other treatments for adults with mCRPC who have received an ARPI and at least one taxane-based chemotherapy, pERC considered the results of sponsor-submitted an indirect comparison. Although, the sponsor's analysis reported that ^{177}Lu vipivotide tetraxetan was more efficacious than radium-223 + BSC, cabazitaxel + prednisone, olaparib, mitoxantrone/placebo + prednisone, and ARPI, the indirect comparison has important limitations that preclude drawing conclusions regarding the comparative efficacy of ^{177}Lu vipivotide tetraxetan versus these relevant comparators for the target patient population.

- **Budget Impact analysis:** Based on drug costs alone, the incremental cost of reimbursing ^{177}Lu vipivotide tetraxetan over the initial 3-year period was estimated to be approximately $69.5M based on an assumed average of 4.54 cycles of ^{177}Lu vipivotide tetraxetan per patient. pERC noted 2 key areas of uncertainty with BIA:
    - **Number of cycles:** If, in practice, all patients received the maximum of 6 cycles of ^{177}Lu vipivotide tetraxetan, the budget impact would be higher than estimated by CADTH.
    - **PSMA test costs:** Due to the lack of flexibility in the sponsor's budget impact model, and uncertainty with the availability and access to PSMA testing, CADTH was unable to provide a robust estimate of the budget impact of reimbursing ^{177}Lu vipivotide tetraxetan on the broader health system. CADTH exploratory analyses suggested estimates ranging from $90M to $142M over the initial 3-year timeframe, though this included the cost of the drug and PSMA testing only and could not consider the infrastructure costs required to address the additional burden of testing.
- **Re-treatment for patients with a favourable response:** The committee discussed the potential for re-treatment for patients who demonstrated a favourable response to the 6-cycle regimen. It was noted the maximum recommended dosage for 177Lu vipivotide tetraxetan is 6 cycles and that there is no evidence to support additional cycles.

Background

Prostate cancer is the most common cancer among Canadian men (excluding non-melanoma skin cancers) affecting 1 in 9 men throughout their lifetime. Prostate cancer represents approximately 20% of all new cancers diagnosed in Canadian men and 10% of cancer deaths in men. An estimated 24,600 men in Canada will be diagnosed with prostate cancer in 2022 and 4,600 men will die from prostate cancer in 2022. Patients who die from prostate have typically progressed to the mCRPC stage, with a 5-year survival rate of approximately 30%. Castration-resistant prostate cancer (CRPC) is defined as disease progression despite castrate levels of testosterone and that may present as either a continuous rise in serum prostate specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.

PSMA is a transmembrane glycoprotein that is highly expressed in prostate cancer cells. ^{177}Lu vipivotide tetraxetan contains the radionuclide lutetium-177 linked to a targeting moiety that binds to PSMA, a transmembrane protein that is highly expressed in prostate cancer cells. Upon the binding of ^{177}Lu vipivotide tetraxetan 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.

^{177}Lu vipivotide tetraxetan injection is indicated for the treatment of adult patients with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) who have received at least one androgen receptor pathway inhibitor (ARPI) and taxane-based chemotherapy.

^{177}Lu vipivotide tetraxetan is administered intravenously (IV) and the recommended dose is 7.4 GBq every 6 weeks (± 1 week) for a total of 6 doses. It is available as a 1,000 MBq/mL solution for injection in single-dose vials containing a total amount of radioactivity of 7.4 GBq ± 10% at the date and time of administration.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of 2 RCTs and an indirect comparison in patients with mCRPC.
- Patient perspectives gathered by patient groups, Canadian Cancer Society (CCS) and Canadian Cancer Survivor Network (CCSN).
- Input from public drug plans and cancer agencies that participate in the CADTH review process.
- 3 clinical specialists with expertise diagnosing and treating patients with prostate cancer.
- Input from 1 clinician group, coordinated by the Canadian Cancer Society.

- A review of the pharmacoeconomic model and report submitted by the sponsor.
- A review of relevant ethical considerations related to ^{177}Lu vipivotide tetraxetan.

Ethical Considerations

Input provided by patient groups, clinician groups, and provincial drug programs, as well as direct engagement with clinical experts and relevant literature, were reviewed to identify ethical considerations relevant to the use of ^{177}Lu vipivotide tetraxetan for the treatment of adults with mCRPC.

- Ethical considerations arising in the context of mCRPC highlight impacts on patients as well as disparities in the incidence, treatment, and outcomes of mCRPC – especially as they affect racialized, transgender and gender non-binary peoples. The treatment space of mCRPC is complex, and while there may be general guidance on the types of interventions that could be useful at different stages, there is currently no optimal treatment sequence. This implies a heavy reliance on clinical expertise and a provider's ability to involve patients in a process of shared decision making. This is particularly important in the context of mCRPC as it is incurable.
- Ethical considerations arising in the evidence used to evaluate ^{177}Lu vipivotide tetraxetan highlight limitations related to the definition of "standard of care" used in the VISION trial, whether the inclusion and exclusion criteria were adequately applied, and the high withdrawal rate from the control arm. It was also indicated that VISION trial participants may not be reflective of those seen in clinical practice, even if clinical experts felt trial data would be generalizable to patients with mCRPC.
- As a radiopharmaceutical with extensive health system resourcing needs, the context of ^{177}Lu vipivotide tetraxetan raises several ethical considerations related to its access and use. The need to confirm PSMA status is a prerequisite to being considered a candidate for ^{177}Lu vipivotide tetraxetan, yet access to PET-CT, and more specifically, PSMA PET-CT is very limited in Canada. The logistics associated with the supply and delivery of ^{177}Lu vipivotide tetraxetan also raise ethical considerations related to equitable access. These challenges of variable access to both PSMA PET-CT and ^{177}Lu vipivotide tetraxetan may make it difficult for clinicians to know when or how to discuss ^{177}Lu vipivotide tetraxetan as a treatment option for patients who might be strong candidates.
- The already limited availability of PET-CT broadly is further narrowed in the context of ^{177}Lu vipivotide tetraxetan, which requires the onsite, or regional, production of radiotracers that can specifically target PSMA+ tumours. Funding the development of further PSMA PET-CT capacity will likely be an extensive financial and logistical burden on the health care system.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

Two patient groups, CCS and CCSN, provided input for the treatment of adult patients with PSMA-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy or who are not medically suitable for taxanes. Patient input was gathered from surveys and interview responses among mCRPC patients and caregivers across Canada in August 2022. Total 27 responses were gathered from the survey (19 from CCS and 8 from CCSN). A total of 7 patients (4 from CCS and 3 from CCSN) in the included submissions had experience with the treatment under review.

Patients noted that mCRPC has a substantial negative impact on their quality of life and ability to perform the activities of daily living, including ability to engage in sexual activity, travel and exercise, fulfill family obligations, maintain mental health, work, conduct household chores, concentrate, spend time with family and friends, fulfill practical needs (e.g., preparing meals, dressing, bathing). Patients can suffer from frequent urination, erectile dysfunction, bone or skeletal pain, hot flashes, weight gain, memory loss and cognitive problems. Patient groups noted that they are seeking access to new treatment options that will prolong life, maintain QoL, delay the onset of symptoms, and improve sexual function. They noted that existing treatment options can be associated with negative side-effects and there is a need for effective and more tolerable treatment options.

Clinician input

Input from clinical experts consulted by CADTH

The clinical experts consulted by CADTH noted that there are limited effective treatments for patients with mCRPC who have progressed following treatment with an ARPI and docetaxel. Overall survival is poor for those who have demonstrated disease that is refractory to multiple treatment options and the symptoms of cancer progression pose a considerable burden for patients. Further standard of care treatments, such as cabazitaxel, are associated with significant toxicities for patients. The clinical experts noted that there is a need for therapies that improve OS and quality of life as compared to current standard of care for this patient population and that are better tolerated and more convenient (e.g., less need for supportive medications, less frequent administration).

The clinical experts noted that ^{177}Lu vipivotide tetraxetan could be considered for patients following disease progression on both an ARPI and docetaxel. The experts noted that there is uncertainty regarding the place in therapy relative to cabazitaxel for those patients who are considered appropriate candidates for treatment with a second chemotherapy regimen. The clinical experts consulted by CADTH also identified the requirement for suitable PSMA-PET expression as per the inclusion criteria of the pivotal trial (VISION) to be a candidate for therapy. The clinical experts noted that ^{177}Lu vipivotide tetraxetan should be discontinued in patients with any of the following: disease progression defined as at least 2 of: sustained PSA rise, clinical progression (sustained, non-analgesic responsive pain, performance status decline), radiographic progression; significant toxicity to the treatment; or worsening performance status (i.e., ECOG performance status ≥ 3).

Clinician group input

Clinician group input was received from Canadian prostate treating clinicians with a special interest in the care of those with metastatic prostate cancer (coordinated by the Canadian Cancer Society). The clinician group stated that there are unmet needs for mCRPC patients and a need for additional lines of therapy that can preserve quality of life and provide meaningful survival benefits for those men with progressive metastatic prostate cancer. The clinician group mentioned that the treatment would be most suited for men with progressive (symptomatic, imaging or biochemical) mCRPC, PSMA expressing metastases based on a diagnostic PSMA targeted PET scan, and with adequate performance status (ECOG 0 to 2) and organ function (liver and bone marrow). The clinician group also pointed out that the most meaningful clinical response to treatment for this disease would be to avoid progression, reflected in stability or improvement in biochemical and imaging biomarkers such as serum PSA and bone scan and CT. The clinician group emphasized that appropriate facilities, certifications, and licensed personnel for delivering unsealed radiopharmaceutical treatments would be needed for a safe delivery of the treatment under review, in addition to the necessity of access to diagnostic PSMA targeted PET for proper patient selection.

Drug Program Input

Table 2. Responses to Questions from the Drug Programs

Drug Program Implementation Questions	Clinical Expert Response
Relevant Comparators	
BSC/BSoC in the VISION trial included abiraterone / enzalutamide, bone-directed therapies (e.g., denosumab, zoledronic acid), corticosteroids, and/or radiation. Cytotoxic chemotherapy, other radioisotopes (e.g., Radium 223), immunotherapy, or investigational agents (e.g., olaparib) were not permitted as comparators. Many of the therapies excluded in the VISION trial are relevant comparators to ^{177}Lu vipivotide tetraxetan in practice. Funded relevant comparators depend upon agents used in prior lines of therapy; comparators include taxane-based chemotherapy, alternate chemotherapy (e.g., carboplatin, mitoxantrone), and abiraterone or enzalutamide. For patients with bone only	pERC and the clinical experts consulted by CADTH agreed that the VISION trial excluded relevant comparators. However, the following were noted: • **Olaparib:** an investigational drug for mCRPC when the VISION trial was initiated (i.e., first patient enrolled in May 2018 and olaparib did not receive regulatory approval in any jurisdiction until May 2020) and this drug is indicated for only a small subset of mCRPC patients (i.e., those with documented deleterious or suspected deleterious germline and/or somatic BRCA or ATM mutations). Therefore, the exclusion of this drug from the BSoC regimen is understandable and not considered to be a

Drug Program Implementation Questions	Clinical Expert Response
metastases, radium 223 is a relevant comparator as well. Olaparib may be a relevant comparator in patients with confirmed BRCA or ATM mutation.	major limitation with respect to generalizability of the study results. • **Radium-223**: indicated only for patients with bone metastases and is not available in all Canadian jurisdictions. • **Alternate chemotherapy regimens**: carboplatin is only used in a small number of patients with neuroendocrine differentiation and mitoxantrone is rarely used in Canadian practice • **ARPI:** abiraterone and enzalutamide are not reimbursed by most of the participating drug programs after disease progression on a previous ARPI.
Considerations for Initiation of Therapy	
Eligible patients have had previous treatment with AR-pathway inhibitors and taxanes and must have castrate-resistant prostate cancer in order to be eligible for lutetium. Are patients eligible for ^{177}Lu vipivotide tetraxetan only if prior ARPI/taxanes were given for mCRPC? Are patients who only received ARPI/taxanes for castrate-sensitive disease eligible for ^{177}Lu vipivotide tetraxetan?	In the absence of high-quality data regarding treatment sequencing, the clinical experts commented that patients who received either ARPIs or taxanes in the castrate sensitive prostate cancer disease state setting would be eligible for ^{177}Lu vipivotide tetraxetan in the mCRPC setting. pERC agreed with the clinical experts and noted that sequential use of different ARPIs would be expected to have limited effectiveness. pERC also noted that it would not be common in Canadian practice for a patient who received docetaxel in the mCSPC setting to be retreated in the mCRPC setting.
Patients required ^{68}Ga-labeled PSMA-11 PET-CT scans in order to confirm PSMA-positive disease eligibility for ^{177}Lu vipivotide tetraxetan. This requires access to/funding for ^{68}Ga 68 and ^{68}Ga-labelled PET-CT, which is not currently available across jurisdictions.	The clinical experts consulted by CADTH noted that PSMA testing via PET-CT is not widely available in Canadian routine practice and typically only performed as part of clinical studies, accessed through private mechanisms, or in very rare cases where there is the potential for another malignant diagnosis and the clinical team requires clarity on the histology of the disease. The experts noted that patients may encounter financial and logistical challenges (e.g., inter-provincial travel to access PSMA testing). PSMA PET-CT was a pre-requisite diagnostic test to determine eligibility for ^{177}Lu vipivotide tetraxetan. pERC agreed with the clinical experts and noted the lack of capacity for additional access to PET-CT resources has limited the adoption of PSMA testing in Canada and is an important barrier to the adoption of ^{177}Lu vipivotide tetraxetan into Canadian practice.
The VISION trial included patients with PSMA-positive mCRPC defined as at least one PSMA-positive metastatic lesion and no PSMA-negative lesions that would be excluded according to protocol criteria. The VISION trial defined PSMA-positive lesions disease as: ^{68}Ga uptake greater than that of liver parenchyma in one or	The clinical experts consulted by CADTH noted that the criteria used in the VISION trial are acceptable for the identification of patients. It was noted that the criteria used in the phase 2 TheraP trial were more restrictive and could be used as alternative criteria; however, the sequential 68Ga-PSMA PET-CT scan followed by a FDG PET-CT scan to determine PSMA

Drug Program Implementation Questions	Clinical Expert Response
more metastatic lesions of any size. PSMA-negative lesions were defined as: PSMA uptake equal to or lower than that of liver parenchyma in any lymph node with a short axis of at least 2.5 cm, in any metastatic solid-organ lesions with a short axis of at least 1.0 cm, or in any metastatic bone lesion with a soft-tissue component of at least 1.0 cm in the short axis. Patients with any PSMA-negative lesions were ineligible. In clinical practice, are eligibility criteria and definitions of PSMA-positive and -negative lesions used in the VISION trial appropriate for identifying the eligible population?	status would pose additional implementation challenges for clinicians and the health system (i.e., resource constraints current limit existing access to PET-CT scans for prostate cancer; the need for 2 diagnostic scans to determine PSMA status pose challenges). pERC agreed with the clinical experts and noted that 87% of patients in the VISION trial were deemed to be PSMA positive based on the inclusion criteria for the study.
The VISION trial stated that patients who had been treated with only a single taxane regimen could only be eligible if the physician deemed them unsuitable to receive a second taxane regimen. What is the definition of “not medically suitable for taxanes”?	pERC and the clinical experts consulted by CADTH noted that patients with the following characteristics would not be medically suited for taxane-based therapy: • ECOG performance status > 2 • Pre-existing peripheral neuropathy > Grade 2 • Contraindications to use of corticosteroid treatment, uncontrolled/active infection • Neutrophil count < 1 x 10^9/L • Platelet count < 75 x 10^9/L • Hemoglobin < 80 g/L • Hyperbilirubinemia > Grade 2 • ALT/AST elevation > Grade 2 • History of pre-existing pneumonitis > Grade 2 • Significant neuro-cognitive disorder and/or lack of patient reliability or social support that leads to risk of toxicities not being reported.
Considerations for Continuation or Renewal of Therapy	
The VISION trial included imaging at baseline, then every 8 weeks for 24 weeks, then every 12 weeks until end of treatment. Radiologic evaluations included CT or MRI and bone scans. Are imaging assessments included in VISION trial appropriate in clinical practice?	The clinical experts noted that the intensity of imaging used in the VISION trial is common in clinical trials for mCRPC but not in routine clinical practice. It is anticipated that imaging for patients with mCRPC would be performed once every 12 weeks in practice or earlier in response to changes in symptoms and/or clinical examination. pERC agreed with the clinical experts and noted that imaging and disease assessment would follow routine clinical practice.
Is there a role for repeat ^{68}Ga-labelled PET-CT to assess treatment response?	The clinical experts noted that the utility of evaluating response to treatment based on repeated ^{68}Ga-labelled PSMA PET-CT assessments was not part of the phase 3 VISION trial and this approach has not been investigated in a prospective, adequately powered fashion. It was noted that the phase 2 TheraP trial included repeat PSMA-PET CT to establish 177Lu retention in target and off-target tissues, with suspension of therapy for patients who demonstration low or no PSMA uptake at sites of metastatic disease; however, no efficacy outcomes were reported based on these subgroups of patients.

Drug Program Implementation Questions	Clinical Expert Response
	pERC agreed with the clinical experts that repeated PSMA PET would not be needed as a standard assessment tool during therapy with ^{177}Lu vipivotide tetraxetan.
Considerations for Discontinuation of Therapy	
VISION trial required patients to have castrate testosterone levels throughout therapy. Is castrate level of testosterone required for continuation of therapy in clinical practice?	The clinical experts consulted by CADTH noted that it is well established in clinical practice to require patients to have castrate levels of testosterone for continuation of systemic therapy. pERC agreed with the clinical experts consulted by CADTH.
Should ^{177}Lu vipivotide tetraxetan be discontinued if testosterone levels are no longer castrate level during therapy?	The clinical experts consulted by CADTH noted that treatment with ^{177}Lu vipivotide tetraxetan should be discontinued if testosterone levels are no longer castrate level after initiating therapy. It was suggested that testosterone levels should be decreased to castrate levels prior to resumption of therapy. pERC agreed with the clinical experts consulted by CADTH.
Considerations for Prescribing of Therapy	
^{177}Lu vipivotide tetraxetan is administered via intravenous infusion at a dose of 7.4 Gb once every 6 weeks for 4 cycles. Up to 2 additional cycles could be administered at the discretion of the treating physician in patients with evidence of disease response. In clinical practice, in which scenarios would two additional cycles be indicated?	The clinical experts noted that the median number of cycles in the VISION trial was 5 (range: 1 to 6) and that 46.5% of patients received 6 cycles. The clinical experts consulted by CADTH noted that evaluating response to treatment for the target patient population (i.e., those with progressive mCRPC) is multifactorial and would be based on clinical response, radiographic imaging, biochemical measures, and need for medications to manage pain. It was noted that a formal assessment of response after 4 cycles (as performed in the VISION trial) is unlikely to be standardized in Canadian clinical practice and could be challenging to implement if included as renewal criteria for ^{177}Lu vipivotide tetraxetan. pERC agreed with the clinical experts consulted by CADTH.
Should ^{177}Lu vipivotide tetraxetan be added to an existing systemic treatment for patients who otherwise meet trial criteria?	The clinical experts consulted by CADTH noted that combination usage in Canada may be limited by reimbursement status. Public reimbursement for ARPIs after a patient has demonstrated disease progression on the therapy varies across jurisdictions, with some provinces mandating discontinuation of coverage and others that may permit continuation of therapy. Overall, the experts noted that it is uncertain if combination usage with ^{177}Lu vipivotide tetraxetan with other systemic anticancer therapies offers additional clinical benefit for patients. pERC agreed with the clinical experts consulted by CADTH and noted that the most frequent scenario would be treatment with

Drug Program Implementation Questions	Clinical Expert Response
	^{177}Lu vipivotide tetraxetan plus ADT alone. The benefit of any combination is highly uncertain.

ADT = androgen deprivation therapy; ALT = alanine aminotransferase; ARPI = androgen receptor pathway inhibitor; AST = aspartate aminotransferase; BSC = best supportive care; BSoC = best standard of care; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FDG = fluorodeoxyglucose; mCRPC = metastatic castration-resistant prostate cancer ; mCSPC = metastatic castration-sensitive prostate cancer; MRI = magnetic resonance imaging; pERC = pCODR Expert Review Committee; PET = positron emission tomography; PSMA = prostate-specific membrane antigen

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

The evidence for the review of ^{177}Lu vipivotide tetraxetan for the treatment of adults with PSMA-positive mCRPC who have received at least one ARPI and taxane-based chemotherapy was derived from a systematic literature review of pivotal and phase III studies supplemented with additional information to address important gaps in the RCT evidence. One RCT met the eligibility criteria for the systematic review. VISION (N = 831) was a phase 3, open-label, RCT conducted to evaluate the efficacy and safety of ^{177}Lu vipivotide tetraxetan administered in addition to BSC/BSoC as compared to BSC/BSoC only. VISION (N = 831) was a phase 3, open-label, RCT conducted to evaluate the efficacy and safety of ^{177}Lu vipivotide tetraxetan in patients with progressive PSMA-positive mCRPC, when administered in addition to BSC/BSoC as compared to BSC/BSoC only. Patients were randomized 2:1 either ^{177}Lu vipivotide tetraxetan plus BSC/BSoC or BSC/BSoC only with allocation stratified by: lactase dehydrogenase (LDH) (≤ 260 IU/L versus > 260 IU/L); presence of liver metastases (yes versus no); ECOG performance status (0 or 1 versus 2); inclusion of novel androgen axis drug in BSC/BSoC (yes versus no).

The VISION trial enrolled patients with PSMA positive, progressive mCRPC (i.e., serum PSA progression, soft-tissue progression, or progression of bone disease) who had received prior treatment with at least 1 ARPI and at least 1 taxane regimen. Patients who had received treatment with only one taxane regimen were required to be medically unsuitable to receive treatment with a second taxane regimen. The trial was limited to those with an ECOG performance status of 0 to 2. PSMA positive patients were identified using ^{68}Ga-PSMA-11 PET/CT scans that were evaluated centrally based on the following criteria:

1. At least one ^{68}Ga-PSMA-11 positive lesion. A PET/CT "positive" lesion was defined as having uptake greater than normal liver parenchyma, whereas a "negative" lesion were those tumors with uptake less than or equal to liver uptake.
2. All lymph nodes that measured ≥ 2.5 cm in short axis had to be ^{68}Ga-PSMA-11 positive
3. All bone metastases with soft tissue component ≥ 1.0 cm in short axis had to be ^{68}Ga-PSMA-11 positive (bone metastases without a soft tissue component or with a soft tissue component of less than 1.0 cm were not considered for PSMA assessment in screening).
4. All solid organ metastases (e.g., lung, liver, adrenal glands, etc.) ≥ 1.0 cm in short axis had to be ^{68}Ga-PSMA-11 positive.

Only patients with at least one PSMA-positive lesion identified on PSMA-PET (i.e., criterion 1) and no negative lesions (i.e., criteria 2 to 4) were to be enrolled in the study, provided all other inclusion/exclusion criteria were met. The sponsor reported that because the patient population in the VISION trial were heavily pre-treated, distinguishing between healed, sclerotic bone metastases or active sclerotic bone disease on CT would have been difficult; therefore, the VISION enrolment criteria focused on aggressive/destructive bone disease with a soft tissue component for determining patient eligibility.

The VISION trial had considerable early withdrawal of consent and a disproportionate dropout in the BSC/BSoC group (patients typically cited disappointment that they would not receive ^{177}Lu vipivotide tetraxetan). This was a major limitation of the study and required the sponsor to introduce protocol amendments that included: increase the overall target sample size; introducing educational measures to try and bolster retaining patients in the comparator group; and, most importantly from a critical appraisal perspective, defining a new analysis set that would be limited to those enrolled after the protocol amendments were introduced (i.e.,

the PFS-FAS set). This new analysis set was used for the primary evaluation of all endpoints except for OS (FAS) and ORR and disease control rate (DCR) which were evaluating using an even smaller subset of patients (i.e., those in the PFS-FAS who had RECIST evaluable disease).

Efficacy Results

The primary and secondary endpoints of the VISON trial were aligned with those recommended by PCWG3 (i.e., OS, rPFS, time to first symptomatic skeletal event (SSE), health-related quality of life, PFS, and biochemical response (e.g., PSA). As noted above, only the analysis of OS was conducted using the FAS data set.

OS: There was a statistically significant improvement in OS for patients in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group compared with those in the BSC/BSoC only group (HR = 0.62; 95% CI, 0.52 to 0.74; p < 0.001). The median OS was 15.3 months (95% CI, 14.2 to 16.9) in ^{177}Lu vipivotide tetraxetan + BSC/BSoC group compared with 11.3 months (95% CI, 9.8 to 13.5) in the BSC/BSoC only group. Subgroup analyses based on the number of prior taxane regimens favoured ^{177}Lu vipivotide tetraxetan + BSC/BSoC versus BSC/BSoC alone for both those with a single prior taxane (HR: 0.59; 95% CI, 0.46 to 0.75) and 2 or more prior taxane regimens (HR: 0.73; 95% CI, 0.53 to 0.99).

rPFS: There was a statistically significant improvement in rPFS for patients in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group compared with those in the BSC/BSoC only group (HR = 0.40; 99.2% CI, 0.29 to, 0.57; p < 0.001). Events of radiographic progression or death were reported for 66.0% of patients in the ^{177}Lu vipivotide tetraxetan group (171 radiographic progression events and 83 deaths) and 47.4% of patients in the BSC/BSoC only group (59 radiographic progression events and 34 deaths). The median rPFS was 8.7 months (95% CI, 7.9 to 10.8) in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group compared with 3.4 months (95% CI, 2.4 to 4.0) in the BSC/BSoC only group. The sponsor reported that median follow-up time for rPFS was greater in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group compared with the BSC/BSoC group (16.4 months and 3.9 months, respectively).

ORR: The ORR was statistically significantly greater in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group compared with the BSC/BSoC group (29.8% versus 1.7%) with an odds ratio of 24.99 (95% CI, 6.05 to 103.24).

Duration of response (DOR): The median DOR in patients who demonstrated a response to treatment (i.e., CR or PR) was 9.8 months (95% CI, 9.1 to 11.7) in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group. Only 2 patients in the BSC/BSoC group demonstrated a response to treatment and only one of those met the criteria for RECIST radiographic progression or death; therefore, the sponsor reported that the median DOR could not be reliably estimated for the BSC/BSoC group.

DCR: The DCR was statistically significantly greater in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group compared with the BSC/BSoC group (89.0% versus 66.7%) with an odds ratio of 5.79 (95% CI, 3.18 to 10.55; p < 0.001).

Time to first SSE: There were 256 events in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group (66.5%; 60 SSE events and 196 deaths) and 137 events (69.9% of patients; 34 SSE events and 103 deaths) in the BSC/BSoC only group. ^{177}Lu vipivotide tetraxetan + BSC/BSoC was associated with a statistically significant reduction in the risk of SSE (or death) as compared to BSC/BSoC alone (HR: 0.5; 95% CI, 0.40 to 0.62).

PFS: Progression events or death were reported for [redacted] of patients in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group ([redacted] radiographic progression, [redacted] clinical progression; [redacted] PSA progression; [redacted] death) and [redacted] of patients in the BSC/BSoC group ([redacted] radiographic progression, [redacted] clinical progression; [redacted] PSA progression; [redacted] death). ^{177}Lu vipivotide tetraxetan + BSC/BSoC was associated with a statistically significant reduction in the risk of radiographic disease progression, clinical progression, PSA progression or death as compared to BSC/BSoC alone (HR: [redacted]; 95% CI, [redacted]; p < [redacted]). The median PFS was [redacted] months (95% CI, [redacted]) in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group and [redacted] months (95% CI, [redacted]) in the BSC/BSoC only group.

PSA levels: The sponsor reported a large disparity across the 2 treatment groups in the proportion of patients who could be evaluated for PSA doubling time (73.8% and 37.8%, respectively). For the subset of patients who could be evaluated, mean PSA doubling time was 20.1 months (95% CI, 11.5 to 28.6) for ^{177}Lu vipivotide tetraxetan and 12.4 months (95% CI, 7.9 to 16.9) for the BSC/BSoC group

Brief Pain Inventory – Short Form (BPI-SF): Worsening in pain intensity was defined as a ≥30% increase from baseline or ≥2-point increase from baseline in the BPI-SF scale at any time up through the end of treatment visit, clinical disease progression, or death. Time to worsening pain was delayed in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group compared with the BSC/BSoC group (HR: 0.52; 95% CI, 0.43 to 0.63; p < 0.001). The median time to deterioration was 5.9 months (4.8, 6.9) in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC arm compared with 2.2 months (95% CI, 1.8 to 2.8) in the BSC/BSoC group.

FACT-P: Time to worsening in FACT-P scores was defined as time from randomization to the first occurring of a ≥10-point decrease in FACT-P total score compared to baseline, clinical disease progression, or death. Total events were similar between the ^{177}Lu vipivotide tetraxetan + BSC/BSoC and BSC/BSoC only groups (87.0% and 85.7%, respectively). Median time to worsening was reduced in those who received ^{177}Lu vipivotide tetraxetan + BSC/BSoC (5.7 months; 95% CI, 4.8 to 6.6) compared with the BSC/BSoC alone group (2.2 months; 95% CI, 1.8 to 2.8) (HR: 0.54; 95% CI, 0.45 to 0.66; p < 0.001).

FACT-G: Time to worsening in FACT-G scores was defined as time from randomization to the first occurring of a ≥10-point decrease in FACT-G total score compared to baseline, clinical disease progression, or death. Median time to worsening was reduced in those who received ^{177}Lu vipivotide tetraxetan + BSC/BSoC (6.6 months; 95% CI, 5.5 to 7.3) compared with the BSC/BSoC alone group (2.4 months; 95% CI, 2.0 to 3.1) (HR: 0.53; 95% CI, 0.44 to 0.65; p < 0.001).

FAPSI-8: Time to worsening in FAPSI-8 scores was defined as time from randomization to the first occurring of a ≥10-point decrease in total score compared to baseline, clinical disease progression, or death. Total events were nearly identical between the ^{177}Lu vipivotide tetraxetan + BSC/BSoC and BSC/BSoC only groups (86.0% and 86.2%, respectively). Median time to worsening in FAPSI-8 was reduced in those who received ^{177}Lu vipivotide tetraxetan + BSC/BSoC (5.9 months; 95% CI, 4.8 to 6.9) compared with the BSC/BSoC alone group (2.0 months; 95% CI, 1.7 to 2.6) (HR: 0.52; 95% CI, 0.43 to 0.64; p < 0.001).

Harms Results

The sponsor reported that the following events were reported more commonly with the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group compared with the BSC/BSoC group (i.e., a difference of ≥10.0% between the groups): fatigue (43.1% versus 22.9%), dry mouth (38.8% versus 0.5%), nausea (35.3% versus 16.6%), anemia (31.8% versus 13.2%), diarrhea (18.9% versus 2.9%), vomiting (18.9% versus 6.3%), thrombocytopenia (17.2% versus 4.4%), lymphopenia (14.2% versus 3.9%), leucopenia (12.5% versus 2.0%), and urinary tract infection (11.0% versus 1.0%).

A greater proportion of patients in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group reported at least one grade ≥ 3 AE compared with the BSC/BSoC group (52.7% versus 38.0%). Grade ≥ 3 events more commonly reported in the ^{177}Lu vipivotide tetraxetan + BSC/BSoC group included: anemia (12.9% versus 4.9%), thrombocytopenia (7.9% versus1.0%), lymphopenia (7.8% versus 0.5%) and fatigue (5.9% versus 1.5%). Spinal cord compression was reported more commonly in the BSC/BSoC treatment group compared with the ^{177}Lu vipivotide tetraxetan + BSC/BSoC (5.4% versus 1.3%). At least one SAE was reported for a greater proportion of patients in the lutetium vipivotide tetraxetan + BSC/BSoC group compared with the BSC/BSoC group (36.3% versus 27.8%). As previous noted, spinal cord compression was reported more commonly in the BSC/BSoC treatment group compared with the ^{177}Lu vipivotide tetraxetan + BSC/BSoC.

Critical Appraisal

Internal Validity

Randomization was stratified by important prognostic factors and the baseline and demographic characteristics were generally well balanced across the ^{177}Lu vipivotide tetraxetan and BSC groups (including for prior systemic anticancer therapy). The sponsor reported that the open-label design was used because blinding would not be practical due to the specialized precautions required for administration of a radiopharmaceutical, the toxicities related to exposure to a radiopharmaceutical, and it would not be appropriate to subject patients who did not receive a radiopharmaceutical to the post-treatment radiation protection protocols (e.g., maintaining physical distancing from family members). Radiographic images were evaluated using BICR and those results were used in the primary evaluations for rPFS and ORR (local assessments were used for patient management and in sensitivity analyses).

The open-label study design contributed to the high rate of early withdrawal for those who were randomized to the BSC/BSoC alone group (i.e., patients were disappointed at not receiving ^{177}Lu vipivotide tetraxetan, leading to a lack of willingness to comply with the

study protocol and/or interest in receiving therapies that were prohibited in the study protocol). The sponsor established corrective actions through a protocol amendment that included site calls to discuss management of control arm patients, investigator letters clarifying study aspects, updates to pre-screening to improve patient education about the trial. After implementation of these measures, the sponsor noted that withdrawal of consent decreased. However, withdrawal rates in the BSC/BSoC group were 56.0% and 16.3% before and after the protocol amendment (respectively), compared with 1.2% and 4.2% in the ^{177}Lu vipivotide tetraxetan group (i.e., although the rate of discontinuation from the BSC/BSoC group improved after the protocol amendment, it remained considerable higher than the rate observed in ^{177}Lu vipivotide tetraxetan group). As a result of the high dropout rate among the BSC/BSoC group, the sponsor also amended the protocol such that all endpoints with the exception of OS, were analyzed using a newly established PFS-FAS dataset, that was composed of patients enrolled after the educational protocol amendments were introduced. The approach used is a method to handle the early withdrawals; however, the analyses based on the PFS-FAS would not likely have followed the intention-to-treat (ITT) principle, which would impact many of the assumptions of the comparisons. This approach was acceptable to the FDA and Health Canada; however, both regulatory agencies stated that the interpretation of the magnitude of the rPFS effect was limited due to a high degree of censoring from early drop out in the control arm (neither the approved US label nor the Canadian product monograph include the effect size for rPFS from the VISION trial).

The high and disproportionate number of patients who withdrew from the control group could bias the study results in favour ^{177}Lu vipivotide tetraxetan as those who remained in the study may have had a poorer prognosis in comparison with those who withdrew and subsequently received treatment with regimens that were not permitted in the VISION protocol. Similarly, those who remained in the trial may have had fewer therapeutic options (e.g., more advanced disease) and may have lacked resources to obtain access to alternative regimens outside of the clinical trial setting (e.g., due to socioeconomic factors).

External validity

The clinical experts consulted by CADTH noted that the baseline and demographic characteristics for the VISION trial are a reasonable reflection of the target patient population in Canada. The clinical experts consulted by CADTH noted that the duration of survival in the control group (i.e., 11.3 months) exceeds what would be anticipated for the target population in Canadian practice. The experts estimated that survival is typically in the range of 6 to 9 months for patients with progressive mCRPC who have demonstrated disease progression following prior treated with both ARPI(s) and taxane regimen(s). It was noted that this commonly observed in PC clinical trials where patients are often healthier with fewer co-morbidities than the overall patient population encountered in routine Canadian clinical practice.

All of the patients included in the VISION trial had prior exposure to at least one taxane regimen. 41.2% of patients had received 2 taxane regimens and 1.0% had received more than 2 taxane regimens at the time of screening. 57.9% of the total study population had been treated with a single taxane at the time of enrolment in VISION and, therefore, should not have been medically suitable to receive another taxane-regimen in accordance with the study protocol. The clinical experts consulted by CADTH noted that this number is greater than would be anticipated in Canadian practice for the target population where approximately 30% to 40% of patients would be considered not medically suitable to receive cabazitaxel. An important limitation with the external validity of the VISION trial was the large proportion of patients who received cabazitaxel in the post-study treatment setting (i.e., as the VISION trial enrolment criteria stated that patients who had received a single taxane regimen must be medically unsuitable for an additional taxane regimen). The clinical experts consulted by CADTH noted that this would not be reflective of Canadian practice where a patient with mCRPC who is considered ineligible for a further taxane regimen is unlikely to become eligible at a later point in time, as this disease is progressive and improvements in functional status or physiological reserve are not anticipated. Other than these issues, the clinical experts noted that the subsequent therapies could be reflective of routine care for patients where there are no other therapies that have been shown to increase OS.

^{177}Lu vipivotide tetraxetan was administered as an add-on therapy in the VISION trial, which included concomitant administration with other systemic cancer therapies. There are no Canadian clinical practice guidelines that address the use of ^{177}Lu vipivotide tetraxetan and the clinical experts consulted by CADTH noted that it is unclear if combination usage of ^{177}Lu vipivotide tetraxetan with other systemic anticancer therapies would be adopted in practice because of uncertainty regarding the additional clinical benefit and harms for patients.

Several potential comparators for ^{177}Lu vipivotide tetraxetan were not permitted within the acceptable BSoC treatment regimes. These including cytotoxic chemotherapy (e.g., cabazitaxel), immunotherapies, and other systemic radio-isotopies (e.g., radium-223, or hemi-body radiotherapy). The rationale provided by the sponsor was that these therapies could confound the analysis of results and systemic anticancer options in the comparator group were limited to hormone therapies, including ARPIs (e.g., abiraterone and enzalutamide). All of the patients enrolled in the trial had prior exposure to novel ARPIs prior to enrolment. This approach may have biased the treatment effects in favour of ^{177}Lu vipivotide tetraxetan, as the majority those in the BSC/BSoC group had already been treated with and demonstrated disease progression on the only systemic therapies that were permitted in the trial.

^{177}Lu vipivotide tetraxetan could be administered for up to 6 cycles in the VISION trial which is consistent with recommendations in the Canadian product monograph. The VISION trial protocol also included an additional step where the patient was to be evaluated by the investigator after 4 cycles for evidence of treatment response (specified as either radiological response, PSA response, or clinical benefit in the opinion of the investigator); signs of residual disease on CT with contrast/MRI or bone scan; and good tolerance of the treatment. Patients meeting all those criteria could receive up to 2 additional cycles at the discretion of the treating physician. The clinical experts consulted by CADTH noted that evaluating response to treatment for the target patient population (i.e., those with progressive mCRPC) is multifactorial and would be based on clinical response, radiographic imaging, biochemical measures, and need for medications to manage pain. It was noted that a formal assessment of response after 4 cycles (as performed in the VISION trial) is unlikely to be standardized in Canadian clinical practice and could be challenging to implement if included as renewal criteria for ^{177}Lu vipivotide tetraxetan. Overall, the clinical experts consulted by CADTH noted that the distribution of doses observed in the VISION is likely an accurate reflection what would occur with Canadian patients as the treatment is generally well tolerated with relatively few AEs leading dose reductions, interruptions, and discontinuations.

Indirect Comparisons

Description of studies

The sponsor-submitted indirect comparison conducted a systematic review and used a Bayesian network meta-analysis (NMA) to evaluate the relative efficacy of ^{177}Lu vipivotide tetraxetan to other comparators including radium-223 + BSC, cabazitaxel + prednisone, olaparib, mitoxantrone/placebo + prednisone, and ARPI for the treatment of patients with pretreated, progressive mCRPC. The NMA was based on a systematic review of the literature and data from [redacted] studies were used to inform the analyses. The efficacy outcomes of interest were rPFS and OS.

Efficacy Results

The sponsor-submitted indirect comparison reported that the results for OS favoured ^{177}Lu vipivotide tetraxetan versus radium-223 + BSC (HR: [redacted]; 95% CrI, [redacted]) and versus ARPI (HR: [redacted]; 95% CrI, [redacted]). The sponsor-submitted indirect comparison reported that the results for rPFS favoured ^{177}Lu vipivotide tetraxetan versus cabazitaxel + prednisone (HR: [redacted]; 95% CrI, [redacted]), mitoxantrone/placebo + prednisone (HR: [redacted]; 95% CrI, [redacted]) and ARPI (HR: [redacted]; 95% CrI: [redacted]). HRs for OS and rPFS were reported as comparator versus ^{177}Lu vipivotide tetraxetan.

Critical Appraisal

Clinical heterogeneity was present in the analysis due to variation in patient characteristics across the included trials. In the absence of statistical adjustment, sensitivity analyses, or subgroup analyses, the potential impact of the between-study heterogeneity cannot be evaluated. The clinical experts consulted by CADTH noted that there was heterogeneity in clinically important patient characteristics (i.e., historical use of chemotherapy, disease severity, and treatment indication); therefore, the indirect comparison may be subject to bias. Of particular concern was that the patients included in the ^{177}Lu vipivotide tetraxetan trial (i.e., VISION) had more severe disease at baseline as indicated by a higher prior treatment count and at least 40% of patients having previously received cabazitaxel prior to enrolment. Inconsistency of the network was not reported, likely due to the limited ability to do so given the network only had one closed loop.

Summary

The sponsor-submitted indirect comparison had several limitations including the lack of reporting certain items that would better inform on the certainty of the indirect evidence. Despite the heterogeneity present for many patient and study characteristics, the

indirect comparison did not adequately conduct sensitivity and subgroup analysis to investigate the root of heterogeneity or conduct a meta-regression that would adjust for effect modifiers that may influence the results. Consequentially, there is substantial uncertainty around the indirect comparison results and firm conclusions cannot be drawn the efficacy of ^{177}Lu vipivotide tetraxetan versus relevant comparators.

Other Relevant Evidence

The inclusion criteria VISION trial specified that patients who were previously treated with docetaxel and considered eligible to receive cabazitaxel were to be excluded from the study. As this population is included in the Health Canada approved indication, CADTH considered this to be an important gap in the evidence and summarized the phase 2 TheraP which enrolled patients with prior exposure to docetaxel and for whom cabazitaxel was considered the appropriate treatment option.

Description of study

TheraP was a multicenter, open-label, phase 2 RCT comparing the activity and safety of ^{177}Lu vipivotide tetraxetan with cabazitaxel in patients with mCRPC. The study was conducted by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group. Similar to the VISION trial, the study enrolled patients with PSMA-positive mCRPC, but the TheraP trial used a more rigorous 2-stage screening process for determining PSMA status:

- **68Ga-PSMA PET-CT:** patients were eligible if they demonstrated a minimum uptake of SUVmax 20 at a site of disease, and SUVmax > 10 at sites of measurable disease ≥10mm.
- **FDG PET-CT:** patients were ineligible if they demonstrated FDG positive with minimal PSMA expression defined as FDG intensity > 68Ga-PSMA activity OR 68Ga-PSMA SUVmax < 10 (i.e., discordant imaging).

Eligible patients were randomized (1:1) to receive either ^{177}Lu vipivotide tetraxetan or cabazitaxel. Randomization was stratified by disease burden (>20 sites versus ≤20 sites as assessed by PSMA PET-CT); previous treatment with enzalutamide or abiraterone; and study site.

Patients who were randomized to receive ^{177}Lu vipivotide tetraxetan received IV infusions once every 6 weeks for a maximum of six cycles. The starting dose was 8.5 GBq and was decreased by 0.5 GBq each subsequent cycle (i.e., not administered at the dosages recommended in the Canadian product monograph, which is 7.4 GBq). Patients in the cabazitaxel group received IV infusions of 20 mg/m² once every 3 weeks for a maximum of ten cycles. Patients enrolled in TheraP continued to receive supportive cancer therapies (e.g., zoledronic acid or denosumab; palliative radiotherapy). An important difference with TheraP compared with VISION is that patients were prohibited from using other systemic anticancer therapy in the TheraP trial (i.e., the study investigated use as monotherapy, which is more reflective of how ^{177}Lu vipivotide tetraxetan would likely be administered in Canadian clinical practice). Patients could receive any treatment after completion or discontinuation of the study drugs at the discretion of the treating clinician(s).

A total of 291 patients were screened for eligibility and 200 patients were randomized. Similar to the VISION trial, there was a greater proportion of patients in the comparator group (in this case cabazitaxel) who withdrew prior to receiving any doses of the study medications (16/101 [15.8%] in cabazitaxel group versus 1/99 [1.0%] in the ^{177}Lu vipivotide tetraxetan group).

Efficacy Results

After 3 years of follow-up, there was no statistically significant difference between ^{177}Lu vipivotide tetraxetan and cabazitaxel for OS (HR = 0.97; 95% CI, 0.70 to 1.4; p = 0.99). Treatment with ^{177}Lu vipivotide tetraxetan was statistically superior to cabazitaxel for the primary endpoint of PSA response (i.e., reduction of ≥50% from baseline) (risk difference: 29%; 95% CI, 16 to 42); PFS (HR: 0.63; 95% CI, 0.46 to 0.86); rPFS (HR: 0.64; 95% CI, 0.46 to 0.88); ORR (relative risk: 2.12; 95% CI, 1.10 to 4.08); PSA PFS (HR: 0.60; 95% CI, 0.44 to 0.83); and Pain PFS (HR: 0.72; 95% CI, 0.53 to 0.97).

Harms Results

Grade 1 or 2 AEs were more commonly reported in the ^{177}Lu vipivotide tetraxetan group compared with the cabazitaxel group (54% versus 40%, respectively) and Grade 3 or 4 AEs were more commonly reported in the cabazitaxel group compared to the ^{177}Lu vipivotide tetraxetan group (53% vs 33%, respectively).

Critical Appraisal

Internal validity

Randomization was stratified based by a different set of baseline parameters compared with the VISION trial (i.e., disease burden based on metastatic sites [>20 sites versus ≤20 sites], whether or not the patient had received previous treatment with enzalutamide or abiraterone, and the study site). Overall, baseline and demographic characteristics were well balanced across the ^{177}Lu vipivotide tetraxetan and cabazitaxel groups in TheraP. Similar to the VISION trial, the study drugs in TheraP were administered in an open-label manner (see prior commentary on rationale for open-label administration). Radiographic images in TheraP were evaluated centrally, but not in a manner that was blinded to the evaluator.

As with the VISION trial, the internal validity of the TheraP trial was limited by the high and disproportionate early dropout in the comparator group (15.8% in cabazitaxel group versus 1.0% in the 177Lu vipivotide tetraxetan group withdrew prior to receiving any doses of the study medications). The rationale provided was similar to VISION (i.e., patient disappointment at not having access to ^{177}Lu vipivotide tetraxetan). As with VISION, the high and disproportionate number of patients who withdrew from the control group could bias the study results in favour ^{177}Lu vipivotide tetraxetan as those who remained in the study may have had a poorer prognosis in comparison with those who withdrew (though the direction and magnitude of any potential bias is uncertain).

TheraP was a phase 2 study that was not designed or powered to evaluate differences between^{177}Lu vipivotide tetraxetan and cabazitaxel for the primary endpoints that are recommended by PCWG3 (e.g., OS). The investigators reported an OS analysis after 3 years of follow-up which noted no statistically significant difference across the 2 treatment groups; however, this analysis may be confounded by cross-over and other potential differences in subsequent therapy setting.

External validity

Unlike the VISION trial, ^{177}Lu vipivotide tetraxetan was administered as monotherapy (as no other systemic anticancer drugs were permitted as part of the study protocol in TheraP). This is likely more generalizable to the Canadian setting as the clinical experts consulted by CADTH noted that ^{177}Lu vipivotide tetraxetan is likely to be used as monotherapy, noting the lack of evidence to evaluate the potential benefits of combination usage; potential for increased drug-related AEs; and the likelihood that reimbursement status would likely be limited to monotherapy.

The comparator in TheraP (cabazitaxel) was highly relevant to the Canadian context for patients who have previously been treated with docetaxel and an ARPI. Unlike the VISION trial, the TheraP study did not include an eligibility criterion that patients must be considered medically unsuitable to receive further treatment with taxane regimen. The maximum number of cycles used in the TheraP trial (i.e., 6 cycles) was consistent with VISION and the Canadian product monograph; however, the dosage strength was not consistent with recommendations in the product monograph. Patients in TheraP received an initial dose of 8.5 GBq which was decreased by 0.5 GBq each subsequent cycle which is not reflective of the standardized dose of 7.4 GBq that is recommended in the product monograph.

PSMA status in the TheraP trial was determined using a 2-stage screening process where patients were initially screened using ^{68}Ga-PSMA PET-CT and then subsequently evaluated using FDG PET-CT. Those who demonstrated discordant imaging between ^{68}GA-PSMA PET-CT and FDG PET-CT (e.g., FDG intensity levels greater than those observed using the ^{68}Ga-PSMA PET-CT) were excluded from the trial. The clinical experts consulted by CADTH noted that the more rigorous criteria applied in the TheraP could help identify patients who may be most likely to response to ^{177}Lu vipivotide tetraxetan; however, the need for 2 diagnostic PET-CT scans to determine PSMA status would likely pose implementation challenges in clinical practice for clinicians and the health system.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population(s)	Patients with prostate-specific membrane antigen positron emission tomography-scan positive mCRPC who have received androgen receptor pathway inhibitor and taxane-based chemotherapy. Aligns with reimbursement request.
Treatment	^{177}Lu vipivotide tetraxetan
Dose regimen	7.4 GBq (i.e., one vial) IV every 6 weeks for up to 6 doses, or until disease progression, or unacceptable toxicity
Submitted price	^{177}Lu vipivotide tetraxetan, 1,000 mbq/ml, vial of solution for IV injection: $27,000
Treatment cost	At the submitted price, and based on the sponsor's assumption of 4.54 cycles per patient per the VISION trial, the treatment cost was $122,489 per patient
Comparator(s)	• BSC/BSoC, as per the VISION trial[a] • Cabazitaxel 60 mg
Perspective	Canadian publicly funded health care payer
Outcome(s)	QALYs, LYs
Time horizon	10 years
Key data source	• VISION trial: efficacy and safety of 177Lu vipivotide tetraxetan vs. BSC/BSoC, health utility values for 177Lu vipivotide tetraxetan and BSC/BSoC • Sponsor-submitted NMA: efficacy of 177Lu vipivotide tetraxetan vs. cabazitaxel • NICE TA391: health utility values for cabazitaxel
Key limitations	• Comparative efficacy of ^{177}Lu vipivotide tetraxetan and relevant comparators is uncertain. As highlighted in the CADTH clinical review, CADTH identified concerns regarding the both the internal and external validity of the VISION results, in particular, imbalanced censoring between patients in ^{177}Lu vipivotide tetraxetan and BSC/BSoC arms may bias the results for rPFS and SSE, favouring ^{177}Lu vipivotide tetraxetan. CADTH also noted uncertainty in the relative efficacy of ^{177}Lu vipivotide tetraxetan and cabazitaxel, due to limitations associated with the sponsor-submitted NMA. Clinical expert feedback indicated that there is no robust evidence that ^{177}Lu vipivotide tetraxetan is more effective than cabazitaxel. • Patient population considered in the sponsor's model represented a portion of patients eligible for ^{177}Lu vipivotide tetraxetan, based on Health Canada approved indication. The efficacy and cost-effectiveness of ^{177}Lu vipivotide tetraxetan for patients who have already been treated with docetaxel and are eligible for cabazitaxel is unknown because this population was excluded from the VISION trial and was not included in the sponsor's economic model. • Long-term survival benefits of ^{177}Lu vipivotide tetraxetan are highly uncertain. Clinical expert feedback indicated that the predicted long-term rPFS and OS, from the sponsor's selected parametric distribution, were overestimated. • The sponsor excluded radium-223 from the submitted economic analysis. Although radium-223 is not widely funded and is indicated for mCRPC patients with symptomatic bone metastases and without visceral metastases, feedback was received that it remains a relevant comparator, where available. • The sponsor's model used health utility values derived from the VISION trial. Given the lack of information on how the sponsor handled dropout and missing data, which is critical given the high rate of dropout observed in patients receiving BSC/BSoC within the trial, these values were highly uncertain.
CADTH reanalysis results	• To derive CADTH's base case, the following key revisions were made: assuming comparable efficacy of ^{177}Lu vipivotide tetraxetan and cabazitaxel, using alternative survival model to predict long-term rPFS and OS, applying state-specific utility values.

Component	Description
	• In CADTH's base case, ^{177}Lu vipivotide tetraxetan was dominated by cabazitaxel as it was more expensive and associated with the same QALYs. A price reduction of at least 92% would be needed for ^{177}Lu vipivotide tetraxetan to be cost-effective compared to BSC/BSoC at a WTP threshold of $50,000 per QALY gained; a price reduction of approximately 82% for ^{177}Lu vipivotide tetraxetan was required for it to achieve cost parity with cabazitaxel. The cost-effectiveness of ^{177}Lu vipivotide tetraxetan was most sensitive to estimates of the relative efficacy of ^{177}Lu vipivotide tetraxetan and cabazitaxel.

BSC = best supportive care; BSoC = best standard of care; ^{177}Lu = Lutetium; ICER = incremental cost-effectiveness ratio; G-CSF= granulocyte colony-stimulating factor; LY = life-year; mCRPC = metastatic castration-resistant prostate cancer; NMA = network meta-analysis; PSM = partitioned survival model; QALY= quality-adjusted life-year; rPFS = radiographic progression-free survival; SOC= best standard of care; WTP = willingness to pay

[a] SOC – referred to as best supportive care, or best standard of care in the VISION trial Clinical Study Report – is as per investigator/physician's choice from the VISION trial. In line with the Clinical Study Report, this included ketoconazole, androgen reducing agents (including any corticosteroid and 5-alpha reductases), abiraterone, enzalutamide, apalutamide or any other novel androgen axis drug radiation in any external beam or seeded form, bone targeted agents including zoledronic acid, denosumab and any bisphosphonates.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the BIA and economic evaluation excluded relevant comparators; the sponsor underestimated the market share of the comparators but including inflated clinical trial market capture; the cost of testing was not considered within the sponsor's BIA; and concomitant treatments in standard care arm, as well as add-on treatments in the comparator arms, were not representative of the treatments used in clinical practice.

CADTH reanalysis included updating relevant treatment costs and dosages, altering market shares of standard care and cabazitaxel, and updating the standard care regimen to include treatments used in clinical practice. Based on these changes, CADTH reanalysis reported that the reimbursement of ^{177}Lu vipivotide tetraxetan for the treatment of PSMA-positive mCRPC would be associated with a budgetary increase of be $13,670,690 in Year 1, $23,120229 in Year 2, and $32,793,211 in Year 3, with a 3-year total incremental cost of $69,584,130.

Exploratory analyses were undertaken to estimate the budget impact of ^{177}Lu vipivotide tetraxetan in the cabazitaxel eligible and ineligible populations; and scenarios in which testing costs are considered. In the exploratory analyses relating to the patient population, based on an assumption that 65% of the population is cabazitaxel-eligible, ^{177}Lu vipivotide tetraxetan was associated with a budget impact of approximately $45,229,685. In patients who are ineligible for cabazitaxel, ^{177}Lu vipivotide tetraxetan was associated with a budget impact of approximately $24,354,446. When testing costs are included, the incremental budget impact of reimbursing ^{177}Lu vipivotide tetraxetan may increase to as much as $142,924,498.

pCODR Expert Review Committee (pERC) Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting Date: January 11, 2023

Regrets

2 expert committee members did not attend.

Conflicts of Interest

None