# Imaging Implementation Advice Panel: Guidance for PSMA-PET Implementation

## Introduction and Background

In 2022, Pluvicto (Lutetium $^{177}$Lu-vipivotide tetraxetan) was approved by Health Canada as the first targeted radioligand therapy for eligible adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have received at least 1 androgen receptor pathway inhibitor and taxane-based chemotherapy.[1,2] The clinical efficacy of Pluvicto was established in the VISION trial, a pivotal, phase III, open-label, randomized controlled trial that compared Pluvicto in addition to best supportive care or best standard of care to best supportive care or best standard of care alone.[3]

CADTH conducted a reimbursement review of Pluvicto,[4] which included comprehensive assessments of the clinical effectiveness and cost-effectiveness, patients' and clinicians' perspectives, and ethical considerations. On March 3, 2023, CADTH issued a final recommendation for the conditional reimbursement of Pluvicto.[5] CADTH also published a report on the infrastructural readiness of Canada's health care system for the adoption of PSMA-PET for the staging and restaging of prostate cancer.[6]

The CADTH recommendation for Pluvicto stated that eligible patients should be identified based on the criteria that were used in the VISION trial. To be eligible for enrolment in the VISION trial, patients were required to undergo PSMA-targeted PET scans with gallium-68 ($^{68}$Ga) gozetotide to determine PSMA-positivity status. At the time of this review, $^{68}$Ga gozetotide is the only PSMA-targeted PET diagnostic agent that has been issued a Notice of Compliance (NOC) by Health Canada, although other PSMA diagnostic agents (i.e., $^{18}$F-DCFPyL and $^{18}$F-PSMA-1007) are currently used in Canada in practice and as part of clinical research protocols.[7-9]

CADTH received stakeholder feedback on the Pluvicto recommendation from nuclear medicine specialists, the manufacturer of the drug, and the participating drug programs. All expressed concerns that there is limited availability of $^{68}$Ga gozetotide in Canada and that other PSMA-targeting diagnostic agents should be considered for the purposes of identifying patients with mCRPC who may be candidates for treatment with Pluvicto.

To examine options regarding alternative PSMA diagnostic agents, CADTH convened an expert implementation advice panel to provide advice on the various PSMA radiopharmaceuticals considered suitable for identifying patient eligibility for Pluvicto. The implementation advice was developed in accordance with the CADTH Procedures for Medical Imaging Implementation Advice.[10]

## Implementation Question

At the request of the CADTH's jurisdictional advisory committee for oncology drugs (the Provincial Advisory Group [PAG]), CADTH convened an implementation advice panel on June 19, 2023, to provide advice for addressing the following implementation question:

- In addition to gallium-68 ($^{68}$Ga) gozetotide, what other PSMA radiopharmaceutical agents are usable in clinical practice to identify patients eligible for treatment with Pluvicto?

## Consultation Process and Objective

The implementation advice panel comprised 6 specialists with expert knowledge of and/or clinical experience with nuclear medicine agents and/or technologies relevant to PSMA-PET imaging and a panel chair. The implementation advice panel members represented various disciplines and clinical settings from across Canada, including radiology, nuclear imaging, nuclear medicine physics, and oncology.

The objective of the panel was to provide expert advice to PAG regarding the implementation of radiopharmaceutical agents other than $^{68}$Ga gozetotide able to determine eligibility for Pluvicto. Stakeholders, including clinicians and pharmaceutical manufacturers, were invited by CADTH to provide input in advance of the panel meeting, and their input was considered by the panel when developing their advice.

Attendance at the implementation advice panel meeting was limited to the panel members and chair, PAG representatives, and key CADTH staff. Expertise for this Medical Imaging Implementation Advice Panel has been drawn from the pan-Canadian network of connections established through CADTH's Canadian Medical Imaging Inventory (CMII).[11] A consensus-based approach was used to guide panel discussions addressing the implementation question.

Following the panel meeting, CADTH staff prepared a summary of the panel's advice, which included consideration of previously received stakeholder input. The final document was informed by additional feedback from both the panellists and stakeholders. The advice provided in this report has been developed from the knowledge and expertise of the implementation panel members and reflects opinions that have been informed by the panellists' experiences and may not necessarily be based on evidence.

## Focus of Report

This report is based on the panel discussion, which centred around the use of the 3 main PSMA-PET radiopharmaceuticals that were identified by stakeholders as being used in clinical practice and/or research protocols in Canada: $^{68}$Ga gozetotide, currently approved by Health Canada (October 14, 2022) and marketed as Illucix[7] and Locametz,[8] and 2 others undergoing investigation in Canada (i.e., $^{18}$F-DCFPyL and $^{18}$F-PSMA-1007). As a result, this report is not inclusive of all PSMA-targeted radiopharmaceuticals but offers an implementation framework for both existing and emerging diagnostic agents.[6]

Table 1 lists the PSMA-PET agents and corresponding preparation kits (brand names) that are primarily used to identify PSMA status and treatment eligibility in Canada.

### Table 1: Approval Status of PSMA-PET Indicated Radiopharmaceutical Agents in Canada

| PSMA-PET agent | Brand name | Approval status in Canada | Manufacturer |
|---|---|---|---|
| $^{68}$Ga gozetotide | Illuccix<br>Locametz | Approved in 2022.<br>Approved in 2023. | Telix Pharmaceuticals Limited<br>Advanced Accelerator Applications |
| $^{18}$F-DCFPyL | Pylarify | Not currently approved in Canada.<br>Listed as investigational by CPDC. Used in Canadian registries and clinical trial research. | Lantheus Holdings, Inc. |
| $^{18}$F-PSMA-1007 | — | Not currently approved as a commercial product in Canada.<br>Licensed for development in Canada. | CPDC from ABX GmbH, Germany |

$^{18}$F-DCFPyL = piflufolastat F-18; $^{18}$F-PSMA-1007 = $^{18}$F(fluoride)-labelled prostate-specific membrane antigen; $^{68}$Ga gozetotide = gallium-68 gozetotide; ABX GmbH = ABX Advanced Biochemical Compounds; CPDC = Centre for Probe Development and Commercialization; PSMA = prostate-specific membrane antigen.

## Summary of Implementation Advice

- All 3 PSMA-PET radiopharmaceuticals ($^{68}$Ga gozetotide, $^{18}$F-DCFPyl, $^{18}$F-PSMA-1007) are appropriate for use in identifying patient eligibility when validated criteria and thresholds are used and image interpretation and assessment are conducted by an appropriately trained PET-interpreting physician.
- The VISION trial criteria used for defining a positive lesion were uptake greater than normal liver parenchyma with $^{68}$Ga gozetotide. Liver parenchyma can be used as a threshold for $^{18}$F-DCFPyl, which exhibits physiological activity in the liver like $^{68}$Ga gozetotide.
- For PSMA-PET radiopharmaceuticals that exhibit higher normal liver uptake or hepatobiliary excretion (e.g., $^{18}$F-PSMA-1007), set detection thresholds are appropriate for confirming PSMA positivity.
- The acquisition and implementation of additional PSMA-PET radiopharmaceuticals are not anticipated to increase the target population or number of patients eligible for Pluvicto beyond those that have been reported by CADTH,[5] although this may change as data emerge to improve methods used to define eligibility criteria.
- There may be opportunities to refine patient cohorts who will most benefit from therapy as evidence matures regarding PSMA-PET eligibility criteria and thresholds.
- System costs associated with PSMA-PET imaging agents for this class of therapy and relevant implementation, capacity, and equity in access factors should be considered for usability in clinical practice.

## Panel Discussion

### PSMA-PET Radiopharmaceuticals Capable of Verifying PSMA Positivity Are Appropriate for Use With Patients With mCRPC

There was consensus among the panellists that there is emerging evidence to support the use of PSMA-PET radiopharmaceuticals other than $^{68}$Ga gozetotide to identify patients eligible to receive treatment with Pluvicto. The panel emphasized that any PET radiopharmaceutical that targets PSMA (e.g., $^{68}$Ga gozetotide, $^{18}$F-DCFPyl, $^{18}$F-PSMA-1007) may be appropriate for use in clinical practice when the following conditions are met:

- PSMA positivity is confirmed using validated criteria and detection thresholds.
- Image interpretation and assessment are conducted by an appropriately trained PET-interpreting physician.

### Considerations for the Application of PSMA-Positivity Defining Thresholds With $^{18}$F-DCFPyL and $^{18}$F-PSMA-1007

One panellist provided a summary of literature on PSMA-PET radiopharmaceuticals and the detection methods that may be used to confirm PSMA positivity. The 2 most frequently reported thresholds discussed for evaluating PSMA-PET radiopharmaceutical uptake included:

- visual comparison with a reference region (e.g., liver, parotids, spleen)
- use of a set (i.e., predetermined) detection threshold, such as the maximum standard uptake value ($SUV_{max}$) (a cut-off value used to provide a semiquantitative measure of radiopharmaceutical accumulation within a region of interest).[12]

The use and implementation of PSMA-PET radiopharmaceuticals other than $^{68}$Ga gozetotide were reviewed. Several studies were discussed that compared the use of $^{68}$Ga gozetotide and $^{18}$F-DCFPyL imaging using both liver reference and $SUV_{max}$ methods for determining PSMA positivity in patients.[13,14] The use of the liver as a reference region is based on the VISION study,[3] in which the presence of at least 1 PSMA-positive metastatic lesion was necessary for treatment eligibility, in addition to other trial requirements which are described elsewhere by CADTH.[5]

The panellist highlighted that both radiopharmaceuticals showed similar biodistribution patterns, liver uptake, and lesion detection.[13,14] It was suggested that:

- $^{68}$Ga gozetotide and $^{18}$F-DCFPyL radiopharmaceutical uptake, measured using the liver as a reference organ or an $SUV_{max}$ threshold, are likely equivalent for the purpose of selecting eligible patients for Pluvicto treatment.
- $^{68}$Ga gozetotide, $^{18}$F-DCFPyl, $^{18}$F-PSMA-1007 are likely comparable for determining PSMA positivity when a set detection threshold (e.g., $SUV_{max}$) is used.

Due to preferential uptake of $^{18}$F-PSMA-1007 in the liver, the panellists cautioned against using the liver as a reference organ for this agent, and instead recommended the use of a numeric detection threshold or

alternative reference organ (e.g., parotids, spleen).[15] The following points were expressed by the panellists regarding threshold selection for confirming PSMA positivity (Table 2):

- The VISION trial criteria (i.e., liver reference) used for defining a positive lesion can be applied to most validated PSMA-PET radiopharmaceuticals that do not demonstrate preferential liver uptake (e.g., $^{68}$Ga gozetotide, $^{18}$F-DCFPyl).
- For agents that exhibit higher than normal liver uptake or hepatobiliary excretion (e.g., $^{18}$F-PSMA-1007), set detection thresholds, such as $SUV_{max,}$ are appropriate for use. $SUV_{max}$ thresholds between 10 and 20 have been used in the literature, but there are currently not enough data to endorse a single value.
- There is evidence to support the use of the parotids as a reference organ for $^{68}$Ga gozetotide, $^{18}$F-DCFPyl, and $^{18}$F-PSMA-1007, and a need to explore alternative reference organs that can be used to determine Pluvicto eligibility.[16]
- There is evidence that the parotids show higher uptake for $^{68}$Ga gozetotide and $^{18}$F-DCFPyl than the liver, making it a potentially more stringent reference organ for determining PSMA positivity; for $^{18}$F-PSMA-1007, liver and parotid uptake may be similar.[16,17]

## Table 2: Panel-Recommended PSMA-Positivity Detection Thresholds for the Main PSMA-PET Indicated Agents in Canada

| PSMA-PET agent | Threshold type | |
|---|---|---|
| | Reference: Liver | Set: $SUV_{max}$ |
| $^{68}$Ga gozetotide | Yes | Yes |
| $^{18}$F-DCFPyL | Yes | Yes |
| $^{18}$F-PSMA-1007 | No | Yes |

$^{18}$F-DCFPyL = piflufolastat F-18; $^{18}$F-PSMA-1007 = $^{18}$F(fluoride)-labelled prostate-specific membrane antigen; $^{68}$Ga gozetotide = gallium-68 gozetotide; PSMA = prostate-specific membrane antigen; $SUV_{max}$ = maximum standard uptake value.

Note: Threshold type refers to use of either the liver as a reference or an $SUV_{max}$ detection threshold to measure PSMA-PET tracer activity of suspected malignant tissues.

## Clinical Expertise Should Inform the Method Used for Measuring PSMA-PET Tracer Uptake in Suspected Malignant Tissues

The panel noted that the type of threshold used to measure PSMA-PET radiopharmaceutical activity and treatment eligibility impacts outcome in clinical practice, including biochemical response to treatment (i.e., ≥ 50% decline in prostate-specific antigen).[18] The panellists emphasized that the threshold for a selected PSMA-PET radiopharmaceutical should be based on an appropriate biochemical response to treatment and patient impact, informed by clinical expertise.

Compared with the use of the liver reference threshold, the use of either a set detection threshold or a threshold 1.5 times greater than the liver threshold has been associated with higher biochemical response rates (e.g., 36% versus 50% to 57% biochemical response).[19] Several panellists expressed that PSMA-PET radiopharmaceuticals measured using a set detection threshold (e.g., $SUV_{max}$) may be equivalent to or have advantages over using a liver reference, although future research is required.

## The Use of Other PSMA-PET Radiopharmaceuticals Is Not Expected to Significantly Change the Patient Population Eligible for Treatment

There was general agreement among the panellists that the acquisition and implementation of additional PET-PSMA radiopharmaceuticals are not anticipated to increase the patient population or number of patients eligible for Pluvicto beyond those that have been reported by CADTH (i.e., 827, 837, and 847 patients in years 1, 2, and 3, respectively),[5] although this may change as data emerge to improve methods used to define eligibility criteria. The following points were commented on by multiple panellists:

- Clinical practice continues to evolve as ongoing evidence emerges to support the refinement of definitions around PSMA positivity thresholds relating to eligible patient populations and outcomes.
- Refinements to PSMA-PET testing will provide opportunities to improve the identification of eligible patient cohorts who will benefit most from therapy.

## Future Implementation Areas of Focus for Emerging PSMA-PET Imaging Agents

There was consensus among the panellists on the importance of considering system-level costs, capacity, and access factors that may impact the future implementation of novel PSMA-PET radiopharmaceuticals in Canada. The following key points were expressed by the panel:

- The availability and use of PSMA-PET agents vary across Canadian jurisdictions, posing important implementation, capacity, and equity considerations.
- A pan-Canadian health technology assessment initiative to assess the system costs and impact of these relatively high-cost, specialized PET-imaging agents would be valuable.
- Updated Canadian PSMA guidelines would help refine the target population for treatment.

# References


1. PluvictoTM (lutetium (177Lu) vipivotide tetraxetan): 1000 MBq/mL at calibration sterile solution for intravenous injection/ infusion [product monograph]. Millburn (NJ): Advanced Accelerator Applications USA; 2022: https://pdf.hres.ca/dpd_pm/00067158.PDF. Accessed 2022 Aug 25.
2. Novartis Pharmaceuticals Communications. Health Canada approves PLUVICTO™ as first targeted radioligand therapy for progressive PSMA positive metastatic castration-resistant prostate cancer. 2022; https://www.novartis.com/ca-en/news/media-releases/health-canada-approves-pluvictotm-first-targeted-radioligand-therapy-progressive-psma-positive-metastatic-castration-resistant-prostate-cancer#:~:text=The%20Health%20Canada%20approval%20of,treated%20with%20BSC%2FBSoC%20alone. Accessed 2023 Jun 30.
3. Sartor O, de Bono J, Chi KN, et al. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2021;385(12):1091-1103. PubMed
4. CADTH. CADTH Reimbursement Review: Lutetium (177Lu) Vipivotide Tetraxetan (Pluvicto). *Can J Health Technol.* 2023;3(5). https://www.cadth.ca/sites/default/files/DRR/2023/PC0297-Pluvicto_combined.pdf. Accessed 2023 Aug 18.
5. CADTH Drug Reimbursement Expert Review Committee final recommendation: Lutetium (177Lu) vipivotide tetraxetan (Pluvicto). Ottawa (ON): CADTH; 2023: https://www.cadth.ca/sites/default/files/DRR/2023/PC0297%20Pluvicto%20-%20Final%20CADTH%20Recommendation%20(with%20redactions)%20March%203%2C%202023_For%20publishing_JH_BMc-meta.pdf. Accessed 2023 Jul 4.
6. CADTH health technology review: prostate-specific membrane antigen PET-CT imaging for the staging of prostate cancer in Canada. *Can J Health Technol* 2022;2(11). https://www.cadth.ca/sites/default/files/attachments/2022-11/CM0001-PSMA-PET3.0-KH-AM-KH-KH2%20-%20with%20updates%20-%20QC-meta.pdf. Accessed 2023 Aug 18.
7. Telix Pharmaceuticals Limited. Health Canada approves Illuccix® for prostate cancer imaging [news release]. 2022; https://telixpharma.com/news-views/health-canada-approves-illuccix-for-prostate-cancer-imaging/. Accessed 2023 Jun 30.
8. Novartis. Locametz® (kit for the preparation of gallium Ga 68 gozetotide injection for intravenous use) 2022; https://www.hcp.novartis.com/products/locametz/psma-pet-ct/. Accessed 2023 Jun 30.
9. Hill S, Vu T, MacDougall D, Picheca L. PET imaging with prostate-specific membrane antigen for prostate cancer: clinical utility. *(CADTH rapid response report: summary of abstracts).* Ottawa (ON): CADTH; 2020: https://www.cadth.ca/pet-imaging-prostate-specific-membrane-antigen-prostate-cancer-clinical-utility. Accessed 2023 Aug 18.
10. CADTH. CADTH procedures for medical imaging implementation advice. 2023; https://www.cadth.ca/sites/default/files/Drug_Review_Process/CADTH_Procedures_Medical_Imaging_Advice.pdf. Accessed 2023 Jun 30.
11. CADTH. Canadian Medical Imaging Inventory. 2022; https://www.cadth.ca/canadian-medical-imaging-inventory. Accessed 2023 Jun 30.
12. Jansen BHE, Kramer GM, Cysouw MCF, et al. Healthy tissue uptake of (68)Ga-prostate-specific membrane antigen, (18)F-DCFPyL, (18)F-fluoromethylcholine, and (18)F-dihydrotestosterone. *J Nucl Med.* 2019;60(8):1111-1117. PubMed
13. Dietlein M, Kobe C, Kuhnert G, et al. Comparison of [(18)F]DCFPyL and [ (68)Ga]Ga-PSMA-HBED-CC for PSMA-PET imaging in patients with relapsed prostate cancer. *Mol Imaging Biol.* 2015;17(4):575-584. PubMed
14. Ferreira G, Iravani A, Hofman MS, Hicks RJ. Intra-individual comparison of (68)Ga-PSMA-11 and (18)F-DCFPyL normal-organ biodistribution. *Cancer Imaging.* 2019;19(1):23. PubMed
15. Eiber M, Herrmann K, Calais J, et al. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): proposed miTNM classification for the interpretation of PSMA-Ligand PET/CT. *J Nucl Med.* 2018;59(3):469-478. PubMed
16. Hotta M, Gafita A, Murthy V, et al. PSMA PET tumor-to-salivary gland ratio to predict response to [(177)Lu]PSMA radioligand therapy: an international multicenter retrospective study. *J Nucl Med.* 2023;64(7):1024-1029. PubMed
17. Giesel FL, Hadaschik B, Cardinale J, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. *Eur J Nucl Med Mol Imaging.* 2017;44(4):678-688. PubMed

18. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol.* 2008;26(7):1148-1159. PubMed

19. Woo S, Ghafoor S, Becker AS, et al. Prostate-specific membrane antigen positron emission tomography (PSMA-PET) for local staging of prostate cancer: a systematic review and meta-analysis. *Eur J Hybrid Imaging.* 2020;4(1):16. PubMed

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein do not necessarily reflect the views of Health Canada, Canada's provincial or territorial governments, other CADTH funders, or any third-party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the *Canadian Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.