pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Lutetium Lu 177 dotatate (^{177}Lu-Dotatate) (Lutathera) **Submitted Reimbursement Request:** For the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumours in adults whose disease has progressed and is unresectable	
Submitted By: Advanced Accelerator Applications	**Manufactured By:** Advanced Accelerator Applications
NOC Date: January 9, 2019	**Submission Date:** July 30, 2018
Initial Recommendation: May 31, 2019	**Final Recommendation:** August 1, 2019

Approximate per Patient Drug Costs	• ^{177}Lu-Dotatate is $35,000 per dose every eight weeks at a dosage of 7.4 GBq (200 mCi) package via intravenous injection over 30 minutes. • The total cost for four doses is $140,000.

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends the reimbursement of ^{177}Lu-Dotatate (Lutathera) for the treatment of adult patients with somatostatin receptor-positive (SSR+) midgut neuroendocrine tumours (NETs) whose disease has progressed on a somatostatin analogue and is unresectable if the following conditions are met:

- cost-effectiveness being improved to an acceptable level
- feasibility of adoption (budget impact) being addressed
- capacity for jurisdictions to have the infrastructure in place to implement ^{177}Lu-Dotatate.

Eligible patients include those with progressed SSR+ midgut (defined as jejunoileum and proximal colon in the NETTER-1 trial) NETs, and good performance status. Treatment with ^{177}Lu-Dotatate should continue until disease progression, unacceptable toxicity or a maximum of four infusions with doses given in eight week intervals (patients with AEs related to treatment with ^{177}Lu-Dotatate can wait up to 16 weeks between treatments to recover from an AE).

pERC made this recommendation because it was satisfied that there is a net clinical benefit of ^{177}Lu-Dotatate in adult patients with progressed somatostatin receptor-positive midgut NETs compared with octreotide LAR based on a statistically significant and clinically meaningful improvement in progression-free survival (PFS). Furthermore, ^{177}Lu-Dotatate is associated with manageable toxicities and no detriment in quality of life (QoL) compared with octreotide LAR.
pERC concluded that ^{177}Lu-Dotatate in patients with SSR+ midgut NETs aligns with the following patient values: it offers an option for disease

control, delays progression with manageable side effects, and has no detriment to QoL.

pERC noted that at the submitted price, ^{177}Lu-Dotatate cannot be considered cost-effective compared with octreotide LAR in patients with SSR+ midgut NETs. pERC also noted that there is a high level of uncertainty in the cost-effectiveness estimates.

pERC highlighted that the potential budget impact of ^{177}Lu-Dotatate for patients with progressed somatostatin receptor-positive midgut NETs is grossly underestimated and will be substantial due to the high cost of the therapy and the number of eligible patients for this treatment. Additionally, pERC had significant concerns about the capacity of jurisdictions to implement ^{177}Lu-Dotatate given the potentially large number of patients eligible for treatment, the complex protocol for administering ^{177}Lu-Dotatate in selected specialized centres, the need for infrastructure to handle the preparation and administration of this therapy, the potential need for additional in-patient hospitalization, and the need for additional resources and coordination of both nuclear medicine and cancer clinics for administering and monitoring treatment. All of these factors contribute to pERC's concern that implementation could lead to significantly increased costs and resource utilization (e.g., nursing, pharmacy, clinic).

pERC does not recommend reimbursement of ^{177}Lu-Dotatate in patients with SSR+ foregut and hindgut NETs whose disease has progressed and is unresectable.

pERC made this recommendation because the Committee was not confident of the net clinical benefit of ^{177}Lu-Dotatate in patients with SSR+ foregut and hindgut NETs, who were not included in the NETTER-1 trial, due to the limitations in the evidence from the available clinical trials. While pERC considered that ^{177}Lu-Dotatate may produce a tumour response in foregut and hindgut NETs, the Committee was unable to determine how it compares with other treatment options with regards to outcomes important to decision-making such as overall survival (OS), PFS, QoL, and safety. pERC concluded that the mechanism of action is a reasonable rationale in determining the potential benefit for ^{177}Lu-Dotatate; however, it cannot be used to extrapolate for important outcomes such as OS, PFS, and QoL.

pERC noted that ^{177}Lu-Dotatate, in patients with foregut and hindgut NETs, aligned with patient values in that it produced an antitumour response, with manageable side effects and offers an additional treatment option. However, the Committee was unable to draw conclusions on the net benefit of ^{177}Lu-Dotatate for patients with foregut and hindgut NETs.

pERC could not draw a conclusion on the cost-effectiveness of ^{177}Lu-Dotatate in patients with foregut and hindgut NETs compared with other available therapies due to the lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness and Budget Impact
Given that pERC was satisfied that there is a net clinical benefit of ^{177}Lu-Dotatate for the treatment of adult patients with somatostatin receptor-positive midgut NETs whose disease has progressed and is unresectable, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and affordability.

Optimal Sequencing of Available Therapies
pERC concluded that the optimal sequencing of therapies for patients with somatostatin receptor-positive midgut neuroendocrine tumours whose disease has progressed and is unresectable is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognized that provinces will need to address optimal sequencing upon implementation of a reimbursement recommendation for ^{177}Lu-Dotatate, and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.

Resource Use and Adoption of Feasibility
pERC noted that the administration of ^{177}Lu-Dotatate is resource-intensive due to the complex preparation and administration of this drug. In addition, pERC noted there are a limited number of specialized centres in Canada that have the infrastructure in place to administer ^{177}Lu-Dotatate. Therefore, pERC noted that jurisdictions will need to consider the significant impacts of additional resources including nursing, pharmacy, and nuclear medicine staff when considering the feasibility of adoption.

Access to ^{177}Lu-Dotatate Beyond Second-Line Treatment
pERC recognized that due to access issues and the potential wait list due to the limited number of available centres that can administer ^{177}Lu-Dotatate, patients may be treated with an alternative second-line therapy upon disease progression on a somatostatin analogue. Therefore, pERC concluded that in the context of limited access to ^{177}Lu-Dotatate, it would be reasonable for jurisdictions to consider offering^{177}Lu-Dotatate beyond second-line therapy for SSR+ midgut NETs.

Possibility of Resubmission to Support Reimbursement for Foregut and Hindgut NETs
pERC considered that the NETTER-1 trial did not include patients with foregut and hindgut NETs. Additionally, pERC considered that randomized controlled trials have been conducted or are currently being conducted evaluating ^{177}Lu-Dotatate in patients with other GEP-NETs, including foregut and hindgut NETs. pERC noted that new clinical trial data comparing ^{177}Lu-Dotatate with current relevant treatments in Canada for patients with progressed foregut and hindgut NETs could form a basis of a resubmission to pCODR if comparative efficacy data important to decision-making, such as PFS, OS and QoL, are available.

Please note: Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

NETs are an uncommon heterogeneous group of malignant neoplasms that arise from neuroendocrine cells, which are distributed widely throughout the body. They most commonly arise in the gastrointestinal tract (48%), lung (25%), and pancreas (9%), but may also rarely develop in many other organs, including the breast, prostate, thymus, and skin. NETs may also be classified by embryologic site of origin as follows: foregut (thymus, esophagus, lung, stomach, duodenum, pancreas), midgut (appendix, jejunum, ileum, cecum, ascending colon), and hindgut (distal bowel and rectum). They may be functional or non-functional depending on their hormone-secreting status. Additionally, over 90% of GEP-NETs have high concentrations of somatostatin receptors (SSR+). Current therapies include surgery, somatostatin analogues (SSAs), targeted therapies (e.g., everolimus, sunitinib), peptide receptor radionuclide therapy, and less commonly cytotoxic chemotherapy. Although metastatic GEP-NETs often have relatively indolent biology, the five-year OS is approximately 50%. Therefore, pERC agreed that there is a need for more effective treatment options that offer prolonged disease control with manageable side effects and without detrimental impact to patients' QoL.

pERC deliberated upon the results of an open-label, randomized, multi-centre, international, phase III trial, NETTER-1, that evaluated the efficacy and safety of ^{177}Lu-Dotatate compared with high-dose octreotide LAR in patients with advanced, progressive, SSR+ GEP-NETs of the midgut (defined as the jejunoileum and proximal colon). pERC discussed that the reimbursement request was broader than the NETTER-1 trial population in that the phase III trial enrolled patients with only SSR+ midgut NETs and did not include patients with SSR+ foregut or hindgut NETs. pERC also considered that there were several issues identified with the NETTER-1 trial in terms of the trial design, conduct, data collection, and data analyses, which required reanalyses, requested by regulatory agencies (FDA and EMA), of the primary and secondary outcomes, to confirm the validity and magnitude of the effect sizes. Despite the issues identified, the Committee noted that the NETTER-1 trial demonstrated an impressive clinically meaningful and statistically significant PFS benefit of ^{177}Lu-Dotatate compared with the octreotide LAR in patients with SSR+ midgut NETs. pERC also noted the trend in OS; however, the Committee recognized that at the interim OS analysis, the median OS was not reached, and the hazard ratio obtained did not reach the level of statistical significance. Therefore, pERC concluded that there is uncertainty in the OS benefit of ^{177}Lu-Dotatate given the immaturity of the data.

pERC also discussed that patients in the NETTER-1 trial had disease progression on octreotide LAR, and that a significant proportion of patients had received systemic therapy other than SSA therapy in both groups. The Committee also noted the Clinical Guidance Panel's (CGP's) opinion and agreed that it would be reasonable to offer ^{177}Lu-Dotatate to patients beyond second-line therapy because of the limited access to ^{177}Lu-Dotatate. Specifically, pERC considered that access to ^{177}Lu-Dotatate may be limited based on the need for specialized centres to administer ^{177}Lu-Dotatate, and that if progression were to occur on SSA therapy, it would be reasonable to treat disease progression with an alternative available therapy prior to initiating ^{177}Lu-Dotatate in the context of barriers to access to treatment.

pERC discussed the safety profile of ^{177}Lu-Dotatate and noted that the incidence of grade 3 and 4 AEs was higher in patients treated with ^{177}Lu-Dotatate compared with patients in the octreotide LAR group and that the most common grade 3 and 4 AEs observed were gastrointestinal and blood disorders. Overall, pERC agreed that the side effects of ^{177}Lu-Dotatate are manageable through appropriate monitoring. Additionally, pERC discussed that QoL was assessed in the NETTER-1 trial, which compared the time-to-deterioration (TTD) between treatment groups. The Committee noted that TTD was significantly longer in the ^{177}Lu-Dotatate treatment group compared with control for domain scales including global health status, physical functioning, role functioning, diarrhea, pain, body image, disease-related worries, and fatigue. pERC noted that it was unclear whether the differences in TTD were clinically meaningful. Overall, the Committee agreed that there appears to be no detriment in QoL with treatment with ^{177}Lu-

Dotatate compared with octreotide LAR. Overall, pERC concluded that there is a net clinical benefit of ^{177}Lu-Dotatate compared with octreotide LAR for patients with progressed midgut NETs, based on a statistically significant and clinically meaningful improvement in PFS, manageable toxicity profile, and the lack of detriment to QoL observed in the NETTER-1 trial.

pERC also deliberated upon the results of a non-randomized, non-comparative phase I/II study, ERASMUS, which evaluated ^{177}Lu-Dotatate in the broader GEP-NETs population (i.e., not limited to midgut NETs), and which included patients with foregut and hindgut NETs. pERC considered that overall, results of the ERASMUS study appear to be consistent with the results from the NETTER-1 trial. pERC discussed the CGP's conclusions that it would be reasonable to extend treatment with ^{177}Lu-Dotatate to other NETs, including foregut and hindgut NETs, based on the findings from the ERASMSUS study and based on the rationale of mechanism of action (biological plausibility) that the clinical benefit is unlikely to differ based on anatomic site for SSR+ disease. However, the Committee noted that with the absence of a comparator and lack of a statistical analysis plan in the ERASMUS study, it is difficult to interpret the results and draw firm conclusions about the safety and efficacy of ^{177}Lu-Dotatate in the broader GEP-NETs population. Overall, pERC agreed that the mechanism of action is a reasonable rationale in determining the potential benefit for ^{177}Lu-Dotatate in patients with foregut and hindgut NETs; however, it cannot be used to extrapolate for important outcomes such as OS, PFS, and QoL. Therefore, pERC could not conclude that there is a net clinical benefit of ^{177}Lu-Dotatate in patients with progressed foregut and hindgut NETs.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the submitter, who disagreed with pERC's Initial Recommendation to not reimburse ^{177}Lu-Dotatate in patients with progressed foregut and hindgut NETs. The submitter noted that the midgut subpopulation is the largest subpopulation of GEP-NETs and that the results observed in the NETTER-1 trial in the midgut subpopulation can reasonably be extrapolated to the broader GEP-NETs population. The submitter noted that extrapolation from the NETTER-1 trial could be justified because subpopulations are too small to conduct controlled trials, midgut tumours are the most prevalent type of GEP-NETs and they share common cell type origin with overexpression of somatostatin receptors. In addition, pERC noted that the submitter and the patient group feedback raised concerns that the pERC recommendation will deny a large number of GEP-NETs patients the opportunity to potentially benefit from treatment with ^{177}Lu-Dotatate.

pERC discussed that the NETTER-1 trial only included patients with midgut NETs and the evidence to inform the broader NET population was based on a non-randomized, non-comparative, phase I/II study (ERASMUS) with no statistical plan, which evaluated ^{177}Lu-Dotatate in the broader GEP-NETs population. pERC acknowledged that ^{177}Lu-Dotatate may produce a tumour response in foregut and hindgut NETs. However, pERC reiterated that it was not confident of the net clinical benefit of ^{177}Lu-Dotatate in patients with foregut and hindgut NETs because of the limitations in the evidence from the available non-comparative, non-randomized study. The Committee also reiterated that the mechanism of action is a reasonable rationale in determining the potential benefit for ^{177}Lu-Dotatate in patients with foregut and hindgut NETs; however, it cannot be used to extrapolate important outcomes such as OS, PFS, and QoL.

Additionally, pERC considered that randomized controlled trials have been conducted or are currently being conducted evaluating ^{177}Lu-Dotatate compared with other therapies in patients with other GEP-NETs, including foregut and hindgut NETs. pERC noted that new clinical trial data comparing ^{177}Lu-Dotatate with current relevant treatments in Canada for patients with progressed foregut and hindgut NETs could form a basis of a resubmission to pCODR if comparative efficacy data important to decision-making, such as PFS, OS, and QoL, are available.

Finally, pERC discussed the submitter's feedback that noted that the Health Canada–approved indication is for the broader GEP-NETs population. pERC noted that the role of regulatory agencies, such as Health Canada, is limited to assessing the safety and activity of a drug. pERC also stressed that its role as a Health Technology Assessment body is to determine the net clinical benefit of a treatment relative to comparators and in consideration of other factors including cost-effectiveness, patient perspectives, and clinical evidence; a decision that is greatly informed by the robustness of the clinical evidence provided.

pERC considered the comparison with octreotide LAR in the NETTER-1 trial to be reasonable in this setting, but also noted that there are other relevant comparators that ^{177}Lu-Dotatate should be compared with. pERC discussed the results of indirect treatment comparisons (ITCs) provided by the submitter, including a mixed treatment comparison (MTC) comparing ^{177}Lu-Dotatate with octreotide and everolimus

for gastrointestinal NETs (GI-NETs), and a matching adjusted ITC (MAIC) comparing ^{177}Lu-Dotatate with placebo, everolimus, and sunitinib for pancreatic NETs (P-NETs), respectively. pERC considered the critical appraisal of the ITCs and noted that, in agreement with the pCODR Methods Team, the substantial heterogeneity between the included studies, the patient populations, and the number of assumptions made in the analyses made the results highly unreliable and uncertain. Therefore, the comparative efficacy of ^{177}Lu-Dotatate with relevant comparators is unknown.

pERC deliberated on patient input from one patient advocacy group. Patient input indicated that patients value effective treatment options that delay disease progression, improve QoL, and control disease symptoms. pERC noted that patient respondents included patients with broader GEP-NETs. The Committee discussed that that the majority of patients who provided patient input had direct experience with treatment with ^{177}Lu-Dotatate. pERC noted that the majority of patients reported that ^{177}Lu-Dotatate reduced disease progression and that they were able to tolerate side effects of the treatment with no negative impact on their QoL. The Committee also considered that patients expressed that the treatment was easier than the lengthy recovery from surgery or the debilitating side effects from chemotherapy. pERC also considered that most of the patient respondents who were treated with ^{177}Lu-Dotatate accessed treatment through a clinical trial or had to access treatment out of country and pay out of pocket. Overall, pERC agreed that ^{177}Lu-Dotatate aligns with patient values in that it is an effective treatment option that delays disease progression and has manageable side effects with no observed detriment to QoL.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the patient group who noted that the pERC Initial Recommendation is too restrictive and that the patient experience from a majority of patient respondents (n = 53) who had experience with treatment with ^{177}Lu-Dotatate supported the use of ^{177}Lu-Dotatate in the broader GEP-NETs population. The Committee appreciated the feedback from the patient advocacy group and considered that there is a need for more effective treatment options for patients with progressed GEP-NETs, including patients with foregut and hindgut tumours. pERC reiterated that it relies on the deliberative framework to guide decision-making. pERC reiterated that it was not confident that the totality of submitted evidence for the broader GEP-NETs population (including foregut and hindgut tumours) demonstrates that ^{177}Lu-Dotatate improves outcomes important to decision-making, such as PFS, OS, and QoL compared with other treatment options. Overall, pERC felt that they did not have sufficient evidence to confirm that ^{177}Lu-Dotatate addresses the key outcomes that patients noted they value.

pERC deliberated on the cost-effectiveness of ^{177}Lu-Dotatate compared with octreotide LAR for the midgut NETs population based on the submitted economic evaluation and the reanalysis provided by the pCODR Economic Guidance Panel (EGP). Overall, pERC agreed with the EGP that it is difficult to estimate the overall incremental cost-effectiveness ratio (ICER) for this patient population. pERC noted that the EGP's lower-bound estimate of the ICER could not be considered cost-effective and that an upper-bound ICER could not be estimated due to the uncertainty in the comparative effectiveness data that informed the economic analysis. pERC discussed that the EGP was unable to explore alternate duration of treatment effects of ^{177}Lu-Dotatate and that the long-term benefit of ^{177}Lu-Dotatate is highly uncertain. The Committee noted the factors that most influenced the incremental cost are drug costs, administration costs, and the time horizon. The factors that most influenced the incremental clinical effect are the time horizon and the utilities post-progression. Overall, pERC agreed with the EGP's reanalysis estimate of the lower-bound ICER and concluded that at the submitted price, ^{177}Lu-Dotatate cannot be considered cost-effective and that a substantial price reduction would be required to improve the cost-effectiveness to an acceptable level. The Committee concluded that there was a high level of uncertainty in the cost-effectiveness estimates.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the submitter who noted that it is inaccurate to state there was excessive uncertainty in the cost-effectiveness estimates. pERC discussed that there were a number of limitations in the submitted economic evaluation as outlined in the pCODR Economic Guidance Report. pERC noted that the follow-up from the NETTER-1 trial was short and that the large part of the estimated benefit of ^{177}Lu-Dotatate was accrued in the extrapolated parts of the survival curves. In addition, pERC restated that the EGP was unable to explore alternate duration of treatment effects of ^{177}Lu-Dotatate and that the long-term benefit of ^{177}Lu-Dotatate is highly uncertain. The Committee reiterated that there was a high level of uncertainty in the cost-effectiveness estimates. Overall, pERC reiterated that ^{177}Lu-Dotatate cannot be

considered cost-effective and that a substantial price reduction would be required to improve the cost-effectiveness to an acceptable level.

In addition, pERC noted that the EGP did not provide reanalysis estimates for the secondary analyses of ^{177}Lu-Dotatate compared with everolimus for the GI-NETs population and ^{177}Lu-Dotatate compared with everolimus and sunitinib for the P-NETs population. The Committee noted that due to the substantial methodological limitations and the assumptions around the clinical effect estimates informing these analyses, the EGP was unable to conduct reanalyses estimates to confidently provide a best estimate for these comparisons. The Committee noted that the submitter's estimates did not consider the fact that everolimus and sunitinib will be available as generic products and considered that the submitted ICERs would likely be higher when the generic products become available.

pERC discussed factors that could impact the feasibility of implementing a conditional reimbursement recommendation for ^{177}Lu-Dotatate for the treatment of progressed midgut NETs. The Committee noted that PAG requested confirmation on the patient population eligible for treatment with ^{177}Lu-Dotatate. Additionally, PAG requested guidance on the appropriateness of re-treatment with ^{177}Lu-Dotatate. pERC noted that the NETTER-1 trial did not provide data on re-treatment with ^{177}Lu-Dotatate; however, it considered that due to access issues to other treatments, clinicians may want to re-treat beyond the total of four doses with ^{177}Lu-Dotatate to avoid disease progression. In addition, pERC discussed PAG's request for guidance on the appropriate sequencing of somatostatin analogues and everolimus with ^{177}Lu-Dotatate. The Committee noted that access to ^{177}Lu-Dotatate may determine the treatment sequence of other available therapies for this patient population. pERC agreed that the optimal sequencing of therapies for patients is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments.

pERC noted additional uncertainty regarding the adoption feasibility with respect to infusion-related resource utilization and the available infrastructure required to implement ^{177}Lu-Dotatate. pERC noted the potentially long and variable wait list to access ^{177}Lu-Dotatate and the resource use associated with this treatment. pERC considered the fact that additional imaging and in-patient hospital admission may be required. In addition, the Committee discussed that the protocol is complex in terms of the timing of administration of amino acid solution and octreotide LAR. The Committee also considered that the funding of radiopharmaceuticals differs from province to province and that some patients may be required to be referred out of province to receive treatment with radiopharmaceuticals which would increase wait times and lead to access issues. Additionally, pERC agreed with PAG that radiopharmaceuticals would be procured by nuclear medicine programs and prepared by nuclear medicine technologists or radiopharmacists (nuclear medicine pharmacists). Radiopharmaceuticals would be administered by nuclear medicine experts in some centres and by radiation oncologists in other centres. PAG noted that administration of ^{177}Lu-Dotatate may be restricted to specialized centres that have the infrastructure to handle, prepare and administer ^{177}Lu-Dotatate in a safe manner. pERC noted that a significant number of additional resources and increased coordination of both nuclear medicine programs and the cancer clinics would be required to administer and monitor treatment with ^{177}Lu-Dotatate. Overall, pERC had significant concerns about the capacity of jurisdictions to implement ^{177}Lu-Dotatate.

Finally, pERC discussed that the submitted budget impact was considerably underestimated because the submitter substantially underestimated the market share of ^{177}Lu-Dotatate. pERC noted that given the clinically meaningful benefit observed with ^{177}Lu-Dotatate, the uptake of this drug would be much higher, leading to the displacement of other available therapeutic regimens. The Committee noted that overall, the potential budget impact of ^{177}Lu-Dotatate would be substantial.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group (Carcinoid Neuroendocrine Tumour Society of Canada [CNETS Canada])
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, [CNETS Canada]
- The PAG
- The submitter [Advanced Accelerator Applications]

The pERC Initial Recommendation was to conditionally recommend reimbursement of ^{177}Lu-Dotatate (Lutathera) for the treatment of adult patients with SSR+ midgut NETs whose disease has progressed on a somatostatin analogue and is unresectable if the following conditions are met:

- cost-effectiveness being improved to an acceptable level
- feasibility of adoption (budget impact) being addressed
- capacity for jurisdictions to have the infrastructure in place to implement ^{177}Lu-Dotatate. pERC did not recommend reimbursement of ^{177}Lu-Dotatate in patients with SSR+ foregut and hindgut NETs whose disease has progressed and is unresectable.

pERC did not recommend reimbursement of ^{177}Lu-Dotatate in patients with SSR+ foregut and hindgut NETs whose disease has progressed and is unresectable.

Feedback on the pERC Initial Recommendation indicated that the submitter agreed in part with the Initial Recommendation. The patient advocacy group disagreed with the Initial Recommendation. PAG agreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of ^{177}Lu-Dotatate (Lutathera) for the treatment of SSR+ GEP-NETs, including foregut, midgut, and hindgut NETs in adults whose disease has progressed and is unresectable.

Studies included: One randomized controlled phase III trial

The pCODR systematic review included one trial, NETTER-1, an ongoing, open-label, randomized, multi-centre (41 centres), international (eight countries) phase III trial that evaluated the efficacy and safety of ^{177}Lu-Dotatate compared with high-dose octreotide LAR in patients with advanced, progressive, SSR+ GEP-NETs of the midgut (defined as the jejunoileum and proximal colon).

Eligible patients were randomized in a 1:1 ratio to receive ^{177}Lu-Dotatate or high-dose octreotide LAR that was stratified by somatostatin receptor scintigraphy (OctreoScan) tumour uptake score (grade 2, 3, and 4), and by length of time patients had been on a constant dose of octreotide (≤ 6 months versus > 6 months).

Treatment with ^{177}Lu-Dotatate consisted of four administrations at a dose of 7.4 GBq (200 mCi) infused intravenously over a 30-minute period every eight weeks, equating to a cumulative radioactivity of 29.6 GBq (800 mCi), unless unacceptable toxicities occurred, centrally confirmed progression was present on imaging, or the patient was unable or unwilling to adhere to trial procedures, withdrawal of consent, or patient death. In addition to ^{177}Lu-Dotatate, patients in the experimental group received best supportive care with octreotide LAR, which was administered intramuscularly 24 hours (30 mg) after each ^{177}Lu-

Dotatate infusion and then monthly after completion of all four infusions. Patients treated with ^{177}Lu-Dotatate also received intravenous amino acid solution administered concomitantly for renal protection. The control group received high-dose (60 mg) octreotide LAR intramuscularly every four weeks. In both treatment groups patients continued the four-week interval administrations of octreotide LAR until the primary outcome was reached or until 72 weeks from randomization after the primary outcome was reached, unless patients progressed or died. Patient crossover was not permitted per protocol; however, for ethical reasons, patients who had progressed were able to receive other available treatments outside of the trial, which included ^{177}Lu-Dotatate.

The pCODR review also provided contextual information on a non-randomized study, ERASMUS, and submitted ITCs comparing ^{177}Lu-Dotatate with other comparators for the GI-NET and P-NET subgroups.

Patient population: Somatostatin receptor-positive, midgut neuroendocrine tumours

Key eligibility included disease progression (RECIST version 1.1) on either computed tomography or magnetic resonance imaging over a maximum period of three years while receiving an uninterrupted dose of octreotide LAR (20 mg to 30 mg every three to four weeks) for at least 12 weeks before randomization; Karnofsky performance status of at least 60; well-differentiated histologic tumour features, defined as a Ki67 index of 20% or less; somatostatin receptors present on all target lesions (as confirmed by blinded independent central review [BICR]); degree of expression was determined by the lesion that had the highest uptake of radiotracer observed on planar somatostatin receptor scintigraphy (OctreoScan) within 24 weeks before randomization. Patients treated with > 30 mg of octreotide LAR within 12 weeks before randomization, or who had received peptide receptor radionuclide therapy at any time, were excluded.

There were a total of 229 patients randomized into the NETTER-1 trial. The median age of patients was 64 years and most trial patients were white (82%), had a mean Karnofsky performance status score of approximately 88%, primary tumours located in the ileum (73%), and presented with metastases in the liver (83%), lymph nodes (62%), or both (typically in the mesentery or retroperitoneum). The majority of patients in both treatment groups had tumours considered low grade by the Ki67 proliferation index (66% in the ^{177}Lu-Dotatate group, and 72% in the control group) and highest grade in terms of uptake of tumour somatostatin radiotracer (grade 4: 61% in the ^{177}Lu-Dotatate group, and 59% in the control group). Most patients had undergone prior surgical resection (80% in ^{177}Lu-Dotatate group, 82% in control group); and a significant proportion of patients had received systemic therapy other than somatostatin analogue therapy (41% in ^{177}Lu-Dotatate group, 45% in control group).

Key efficacy results: Statistically significant and clinically meaningful improvement in PFS; Immature OS data

The key efficacy outcome deliberated by pERC included the primary end point, PFS by BICR, and secondary end points including OS, QoL, and safety.

At the time of the primary efficacy analysis a total of 91 PFS events had occurred in the trial; 23 in the ^{177}Lu-Dotatate group and 68 in the control group. Median PFS had not been reached in the ^{177}Lu-Dotatate group and was 8.4 months (95% confidence interval [CI], 50.0 to 76.8) in the control group. The hazard ratio (HR) for PFS by BICR was 0.21 (95% CI, 0.13 to 0.33; $P < 0.001$), which indicated a statistically significant improvement in PFS (or a 79% reduction in the risk of a PFS event) in the ^{177}Lu-Dotatate group compared with the control group. Correcting for data errors had a limited impact on the HR (HR = 0.18; 95% CI, 0.11 to 0.29; $P < 0.0001$), and the results remained statistically significant in favour of treatment with ^{177}Lu-Dotatate compared with control therapy. The results of exploratory subgroup analyses performed by baseline characteristics demonstrated a consistent treatment benefit in favour of ^{177}Lu-Dotatate compared with control, where the magnitude of HRs (treatment effect) ranged from 0.14 to 0.24, with no upper bounds of associated CIs crossing unity.

The primary outcome obtained statistical significance at the primary analysis, and therefore the secondary outcomes of objective response rate (ORR) and OS were formally and sequentially tested. At the primary efficacy analysis (interim OS analysis), and prior to data corrections, an HR of 0.40 (95% CI, 0.21 to 0.77; $P = 0.004$) was obtained that did not reach the level of statistical significance pre-specified by the O'Brien-Fleming alpha spending boundary ($P = 0.0085$). A corrected interim analysis of OS produced an HR of 0.46 (95% CI, 0.25 to 0.83; $P < 0.0083$) based on 48 deaths; 17 and 31 in the ^{177}Lu-Dotatate and control groups, respectively. An updated exploratory analysis of OS was performed based on 71 deaths; median OS was still unreached in the ^{177}Lu-Dotatate group and was 27.4 months in the control group (HR = 0.54; 95% CI, 0.33 to 0.86). The final analysis of OS is expected after 158 deaths have accrued.

In response to the pERC Initial Recommendation, the submitter provided feedback noting that, while the OS data remains immature, a statistically significant OS benefit has been shown in a corrected interim analysis (HR = 0.46; 95% CI, 0.25 to 0.83; *P* < 0.0083).

The pCODR methods team confirmed that during the review it requested that the submitter clarify whether the *P* value was considered statistically significant for the corrected interim analysis of OS. The submitter provided a response confirming that the *P* value at the corrected interim analysis was *P* = 0.0083 (unstratified log-rank test) and that the pre-defined threshold was 0.0085% = 0.000085. Since the *P* value exceeded the threshold, the test was not considered significant.

Patient-reported outcomes: TTD significantly longer in ^{177}Lu-Dotatate treatment group compared with control for some domain scales

At the June 30, 2016, data cut-off date, TTD (≥ 10 points change compared with baseline score) was significantly longer in the ^{177}Lu-Dotatate treatment group compared with control for domain scales, including global health status scale: 22.7 months (HR = 0.41; 95% CI, 0.24 to 0.69; *P* < 0.001); physical functioning: 13.7 months (HR = 0.52; 95% CI, 0.30 to 0.89; *P* = 0.015); role functioning: not estimable due to median not reached in the ^{177}Lu-Dotatate group (HR = 0.58; 95% CI, 0.35 to 0.96; *P* = 0.03); diarrhea: not estimable due to median not reached in either treatment group (HR = 0.47; 95% CI, 0.26 to 0.85; *P* = 0.011); pain: 3.7 months (HR = 0.57; 95% CI, 0.34 to 0.94; *P* = 0.025); body image: not estimable due to median not reached in control group (HR = 0.43; 95% CI, 0.23 to 0.80; *P* = 0.006); disease-related worries: 5.8 months (HR = 0.57; 95% CI, 0.36 to 0.91; *P* = 0.018); and fatigue: 0.9 months (HR = 0.62; 95% CI, 0.42 to 0.96; *P* = 0.030).

Limitations of the QoL analysis include a lack of adjustment for multiple testing (which raises the possibility of type I error), uncertainty related to the clinical significance of some of the statistically significant results, and concerns over the reliability of the estimates obtained given the small numbers of patients at risk in both treatment groups for the majority of time points (across domain scales).

Safety: Higher grade 3 and 4 AEs in the ^{177}Lu-Dotatate group

Based on the primary analysis data cut-off date of July 24, 2015, AEs of any grade occurred in 95% of patients in the ^{177}Lu-Dotatate and 86% of patients in the control group. AEs judged by investigators to be related to study treatment occurred in higher frequency in the ^{177}Lu-Dotatate group at 86% versus 31% in the control group. Treatment-related serious AEs were also higher in the ^{177}Lu-Dotatate group (9% versus 1% in the control group). Treatment discontinuation due to treatment-related AEs occurred in 5% of patients in the ^{177}Lu-Dotatate group compared with 0% in the control group.

The most common class of AEs observed in both treatment groups was gastrointestinal disorders; however, the incidence of nausea and vomiting was significantly higher in patients treated with ^{177}Lu-Dotatate occurring in 59% and 47% of patients, respectively, versus 12% and 10% in control patients. The majority of these events were low grade in severity and were attributed to amino acid infusions administered concomitantly with ^{177}Lu-Dotatate. The incidence of grade 3 and 4 AEs was also higher in patients treated with ^{177}Lu-Dotatate (41%) compared with patients in the control group (33%). Of note, grade 3 and 4 hematologic events were only observed in the ^{177}Lu-Dotatate group and included lymphopenia (9%), thrombocytopenia (2%), and neutropenia (1%). Myelodysplastic syndrome (MDS), an AE of special interest, was suspected in one patient with a history of monoclonal gammopathy who underwent bone marrow biopsy and had significant cytopenias consistent with MDS.

Limitations: Several issues with trial conduct, data collection and inappropriate data analysis

The NETTER-1 trial had several limitations, which mainly stemmed from issues with trial conduct and data collection, and inappropriate data analysis approaches. These limitations were considered significant in terms of their potential to affect the internal validity of the trial and prompted reanalyses of the NETTER-1 trial data that incorporated data corrections, more rigorous approaches of analysis, and multiple sensitivity analyses. The reanalyses performed confirmed the validity of the highly statistically significant large effect size that was obtained for the primary outcome at the primary analysis with ^{177}Lu-Dotatate relative to control therapy with octreotide LAR. Other limitations identified include the fact that the trial limited enrolment to patients with GEP-NETS of the midgut and did not evaluate the efficacy of ^{177}Lu-Dotatate in patients with other GI-NET tumours (foregut, hindgut) and other GEP-NET tumour locations (pancreas, lung). In addition, the use of an open-label trial design, where patients were aware of their

treatment assignment, influenced the reporting of patient-reported outcomes in favour of the experimental treatment group.

ERASMUS study: The CGP identified a relevant study, the ERASMUS study, a phase I/II non-randomized, open-label study that evaluated the safety and efficacy of ^{177}Lu-Dotatate in patients with SSR+ GEP-NETS that included multiple tumour types, including P-NETs, foregut, including bronchial NETs, midgut NETs, and hindgut NETs. The study enrolled 1,214 patients between January 2000 and December 2012. The primary end point was ORR. The ORR was 41.2% (95% CI, 37.2 to 45.2), median PFS was 28.0 months (95% CI, 25.0 to 30.3), and median OS was 64.6 months (95% CI, 57.0 to 73.8). The investigators concluded that ^{177}Lu-Dotatate was beneficial to patients with GEP-NETs. While the ERASMUS study suggests that ^{177}Lu-Dotatate may be efficacious for multiple GEP-NET subtypes, the results should be interpreted with caution due to the trial limitations such as the absence of an active comparator and the absence of a statistical analysis plan.

Comparator information: Comparative effectiveness of ^{177}Lu-Dotatate compared with relevant comparators is unknown

The comparison with octreotide LAR in the NETTER-1 trial was considered to be reasonable in this setting; however, there are other relevant comparators that ^{177}Lu-Dotatate should have been compared with. The submitter provided ITCs, including an MTC comparing ^{177}Lu-Dotatate with octreotide LAR and everolimus for GI-NETs, and a MAIC comparing ^{177}Lu-Dotatate with placebo, everolimus, and sunitinib for P-NETs, respectively. The results from the MTC demonstrated that there were no significant differences between ^{177}Lu-Dotatate and relevant comparators in terms of PFS and OS. In addition, the MAIC analysis demonstrated that ^{177}Lu-Dotatate was superior to everolimus, sunitinib, and placebo in terms of OS and PFS. The pCODR Methods Team identified several limitations in the analyses, including the substantial heterogeneity between the included studies and the patient populations as well as the number of assumptions made in the analyses that made the results highly unreliable and uncertain. Overall, the comparative efficacy of ^{177}Lu-Dotatate with relevant comparators is unknown.

Need and burden of illness: Need for more effective alternative treatments that delay progression

NETs are an uncommon heterogeneous group of malignant neoplasms that arise from neuroendocrine cells, which are distributed widely throughout the body. They most commonly arise in the gastrointestinal tract (48%), lung (25%), and pancreas (9%), but may also rarely develop in many other organs, including the breast, prostate, thymus, and skin. NETs may also be classified by embryologic site of origin as follows: foregut (thymus, esophagus, lung, stomach, duodenum, pancreas), midgut (appendix, jejunum, ileum, cecum, ascending colon), and hindgut (distal bowel and rectum). They may be functional or non-functional depending on their hormone-secreting status. Additionally, over 90% of GEP-NETs have high concentrations of somatostatin receptors (SSR+). Current therapies include surgery, SSAs, targeted therapies (e.g., everolimus, sunitinib), peptide receptor radionuclide therapy, and less commonly, cytotoxic chemotherapy. Although metastatic GEP-NETs often have relatively indolent biology, the five-year OS is approximately 50%. Therefore, there is a need for more effective alternative treatment options that offer prolonged disease control with manageable side effects and without detrimental impact to patients' QoL.

Registered clinician input: None received

There was no clinician input received for this review.

PATIENT-BASED VALUES

Experiences of patients with GEP-NETs: Need for more effective treatment options

Patient input from Carcinoid Neuroendocrine Tumour Society of Canada reported the following as key concerns patients have with GEP-NETs: QoL is negatively affected, decreased energy levels and emotional health issues, lifestyle changes on diet and physical activity, inability to work, and increased time and money spent on appointments. Respondents indicated that current therapies for GEP-NETs include surgery, SSA, chemotherapy, and alternative therapies that provide only short-term benefits. The patient respondents included patients with GEP-NETs, including P-NETs and GI-NETs. It was unclear how many patients had midgut NETs.

Patient values on treatment: Stop disease progression, alternative treatment options, improved QoL, and symptom control

Patient respondents indicated that they value effective treatment options to slow disease progression, improve QoL, and control cancer symptoms. The majority of respondents (n=53) reported direct experience with ^{177}Lu Dotatate. Ninety-four per cent of patients who were treated with ^{177}Lu-Dotatate reported that they accessed the treatment through a clinical trial or had to travel out of country. Overall, patients reported that they were able to tolerate and manage the side effects of treatment with minimal negative impact on their QoL. Patients also expressed that the treatment was easier than the lengthy recovery from surgery (ablative, debulking, resection) or the debilitating side effects from chemotherapy.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

The economic analysis submitted included three analyses:

- primary analysis comparing ^{177}Lu-Dotatate with octreotide LAR for midgut NET
- secondary analysis comparing ^{177}Lu-Dotatate with octreotide LAR and everolimus for GI-NETs
- secondary analysis comparing ^{177}Lu-Dotatate with everolimus and sunitinib for P-NETs.

Basis of the economic model: Partitioned survival model

This partitioned survival model was comprised of three health states: stable disease, progressed disease, and death. All patients start in the stable PFS health state. Transitions from one health state to the next were unidirectional. PFS included both on treatment and off treatment.

Key efficacy data sources included: NETTER-1 trial for midgut NET for the primary analysis; submitted ITCs for the GI-NET and P-NET secondary analyses. Utility data were based on utilities collected in the NETTER-1 and ERASMUS trials.

Costs considered included drug costs, supportive medications (including amino acids, rescue subcutaneous octreotide), administration and monitoring costs, AE costs, and end-of-life care costs.

Drug costs: High cost of ^{177}Lu-Dotatate

The list price of ^{177}Lu-Dotatate is $35,000 per dose at a dosage of 7.4 GBq (200 mCi) package via intravenous injection over 30 minutes every eight weeks. The total cost for four doses is $140,000.

The list price of octreotide LAR 60 mg is $4,044.00 per dose at a dosage of 60 mg every four weeks via intramuscular injection.

The list price of octreotide LAR 30 mg is $2,022.00 per one injection dose.

The list price for everolimus is $186.00 at a dose of 10 mg daily. The total cost for 28 days is $5,028.00.

The list price for sunitinib is $186.46 at a dose of 37.5 mg daily. The total cost for 28 days is $5,220.88.

Clinical effect estimates: Considerable uncertainty in the comparative effectiveness data

The submitted model extrapolated the trial data over 20 years and provided two options for parametric survival curves. The EGP was restricted in its ability to conduct scenario analyses to assess alternate duration of treatment effect, the extrapolation of OS and unable to modify the hazard ratio. In addition, the EGP was unable to modify the proportion or types of subsequent treatments in the submitted model. The factors that influenced the incremental cost are drug costs, administration costs, and the time horizon. The factors that most influenced the incremental clinical effect are the time horizon and the utilities post-progression.

Cost-effectiveness estimates: High lower-bound estimate at the submitted price; Upper-bound not estimable

The EGP's lower-bound estimate was higher ($87,155 per quality-adjusted life-year [QALY]) than the submitter's best estimate ($74, 828 per QALY). The EGP's upper-bound estimate is not estimable due to

the uncertainty around the long-term clinical effectiveness because of the long extrapolation based on short follow-up and the EGP's inability to explore alternatives to the duration of treatment effect.

The EGP's lower-bound ICER was based on the following assumptions that were supported by the CGP: a time horizon of 10 years, which appropriately reflects a time horizon for a progressed patient population compared with the 20-year time horizon in the submitted model; and the assumption that 5% of all patients would receive rescue subcutaneous octreotide compared with the 40% assumption in the submitted model.

The submitter provided feedback on the pERC Initial Recommendation noting that it is inaccurate to state that the primary analysis is subject to excessive uncertainty. The results were reported for the entire time horizon and also for the progression-free period only. The EGP has reiterated the number of limitations identified in the primary analysis of the midgut. Notably, the median duration of follow-up from the NETTER-1 trial was short (< 15 months). In the submitted base case, the submitter extended effectiveness estimates observed to a 20-year time horizon. A large part of the estimated benefit of ^{177}Lu-Dotatate is being accrued in the extrapolated parts of the survival curves. Further, the median OS was not reached in the trial. As the submitted model did not include scenario analyses or the capacity to explore declining clinical effectiveness over time, the EGP elected to explore shorter time horizons as an alternate of truncating treatment benefit duration. This was a reasonable alternate approach to address the uncertainty with the data. Due to several restrictions in the submitted model, the EGP was unable to assess alternative durations of treatment effect and the extrapolation of overall survival. Overall, there is considerable uncertainty in clinical effectiveness estimates, including duration of treatment effect and long-term extrapolation from relatively short-term results.

The EGP could not estimate an ICER for the secondary analyses of the GI-NET and P-NET subgroups due to the limitations in the submitted clinical effectiveness data resulting in excessive uncertainty.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact is substantially underestimated

PAG requested confirmation on the patient population eligible for treatment with ^{177}Lu-Dotatate. Additionally, PAG requested guidance on the appropriateness of re-treatment with ^{177}Lu-Dotatate. The NETTER-1 trial did not provide data on re-treatment with ^{177}Lu-Dotatate; however, due to access issues to other treatments, clinicians may want to re-treat with ^{177}Lu-Dotatate to avoid disease progression. In addition, PAG requested guidance on the appropriate sequencing of somatostatin analogues and everolimus with ^{177}Lu-Dotatate.

PAG noted the potentially long and variable wait list to access ^{177}Lu-Dotatate and the resource use associated with this treatment, including additional imaging and the potential need for in-patient hospital admission. In addition, PAG noted that the protocol is complex in terms of the timing of administration of amino acid solution and octreotide LAR.

Funding of radiopharmaceuticals differs from province to province and some patients may be required to be referred out of province to receive treatment with radiopharmaceuticals, which would increase wait times and lead to access issues. Additionally, radiopharmaceuticals would be procured by nuclear medicine programs and prepared by nuclear medicine technologists or radiopharmacists (nuclear medicine pharmacists). Radiopharmaceuticals would be administered by nuclear medicine experts in some centres and by radiation oncologists in other centres. PAG noted that administration of ^{177}Lu-Dotatate may be restricted to specialized centres that have the infrastructure to handle, prepare, and administer lutetium in a safe manner.

The submitted budget impact results for the broader GEP-NETs were taken from a national perspective. The submitter did not provide a midgut specific analysis. The budget impact analysis was considerably underestimated because the submitter underestimated the market share of ^{177}Lu-Dotatate and the potential number of eligible patients for this treatment.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Anil Abraham Joy, who was not present for the meeting
- Daryl Bell, who did not vote due to his role as a patient member alternate.

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Kelvin Chan and Dr. Winson Cheung who were not present for the meeting.
- Daryl Bell, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of ^{177}Lu-Dotatate for gastroenteropacreatic neuroendocrine tumours, through their declarations, five members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting. For the Final Recommendation, five members had a real, potential, or perceived conflict, and based on application of the pCODR Conflict of Interest Guidelines, none of the members were excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
Currently Funded Treatments • Sunitinib and everolimus are funded in all provinces, except for PEI, for pancreatic NET. Everolimus for non-functional NET of gastrointestinal and lung origin is funded in some provinces. • Octreotide LAR is funded in all provinces, except PEI. Lanreotide is listed on provincial drug formularies in some provinces. In most provinces, lanreotide is funded for treatment of acromegaly, but not for NET.	• The submitter provided ITCs comparing ^{177}Lu-Dotatate with relevant comparators for subgroups such as GI-NETs and P-NETs. Specifically, everolimus for GI-NETs and sunitinib and everolimus for P-NETs. Overall, pERC noted that there is substantial heterogeneity between the included studies, the patient populations, and the number of assumptions made in the ITCs, which made the results highly unreliable and uncertain. Therefore, the comparative efficacy of ^{177}Lu-Dotatate with relevant comparators is unknown.
Eligible Patient Population • PAG is seeking confirmation that ^{177}Lu-Dotatate would be for patients with advanced, progressive, well-differentiated, somatostatin receptor-positive midgut neuroendocrine tumours who have had disease progression during somatostatin analogue therapy as in the trial. Clarity on the eligible patients and types of NET would facilitate implementation. • In the trial, eligibility was restricted to patients who progressed on octreotide LAR and patients could not have been treated with more than 30 mg of octreotide LAR at three- or four-week intervals within 12 weeks prior to randomization. PAG noted that some patients are being treated with octreotide LAR at 60 mg. PAG is seeking guidance on whether patients previously treated with lanreotide would be eligible or not for treatment with ^{177}Lu-Dotatate, noting that this may be out of scope of this review and a review of lanreotide for treatment of NET may be required for funding consideration. • PAG is seeking guidance on if and when re-treatment and re-challenge with lutetium would be appropriate.	• Treatment with ^{177}Lu-Dotatate should be limited to patients with progressed midgut NETs, defined as jejunoileum and proximal colon in the NETTER-1 trial. • pERC could not conclude that there is a net clinical benefit of ^{177}Lu-Dotatate in patients with progressed foregut and hindgut NETs based on the available clinical trials. • pERC noted that some patients may be treated with a higher dose of octreotide LAR at 60 mg and agreed with the CGP's opinion that these patients would be eligible for treatment with ^{177}Lu-Dotatate. • pERC noted that the CGP felt it would be reasonable to extend ^{177}Lu-Dotatate to patients with midgut NETs who were previously treated with lanreotide. pERC noted that lanreotide is listed on provincial drug formularies in some provinces; however, in some provinces lanreotide is not publicly funded for NETs. • pERC noted that the NETTER-1 trial did not provide data on re-treatment with ^{177}Lu-Dotatate. However, pERC noted the CGP's expert opinion that clinicians would want to re-treat with ^{177}Lu-Dotatate on a case-by-case basis depending on the degree of response and eligibility for re-treatment based on clinical factors such as renal and hematologic function.
Implementation Factors • PAG noted that the oversight and funding of radiopharmaceuticals differs from province to province. In some provinces, patients may referred out of province to receive treatment with radiopharmaceuticals, where wait times and access could be issues. • PAG noted that radiopharmaceuticals would be procured by nuclear medicine	• pERC noted additional uncertainty regarding the adoption feasibility with respect to infusion-related resource utilization and the infrastructure required to implement ^{177}Lu-Dotatate. • pERC noted the potentially long and variable wait list to access ^{177}Lu-Dotatate and the resource use associated with this treatment. The Committee considered the fact that there would be additional imaging and there may be additional in-patient hospital admission required.

programs and prepared by nuclear medicine technologists or radiopharmacists (nuclear medicine pharmacists). Radiopharmaceuticals would be administered by nuclear medicine experts in some centres and by radiation oncologists in other centres. PAG noted that administration of lutetium may be restricted to specialized centres that have the infrastructure to handle, prepare, administer, and dispose of ^{177}Lu-Dotatate in a safe manner. Additional resources and coordination of both nuclear medicine physician and medical oncologist are required for monitoring, which includes increased blood work monitoring. • Other implementation factors that need to be taken into consideration include amino acid solution and octreotide LAR that are administered with lutetium, additional imaging, and in-patient hospital admission for the first dose. PAG also identified that the protocol is complex with the timing of administration of the amino acid solution and octreotide LAR. • For patients who are on more than 30 mg of octreotide (or 120 mg of lanreotide) every three or four weeks, the doses of octreotide (or lanreotide) would likely be reduced when initiating lutetium. PAG is seeking confirmation of the maintenance dose of octreotide LAR (or lanreotide) when administered in conjunction with lutetium, or whether somatostatin analogues could be discontinued in some cases when a patient is receiving lutetium.	• In addition, the Committee discussed that the protocol is complex in terms of the timing of administration of amino acid solution and octreotide LAR. • The Committee also considered that the funding of radiopharmaceuticals differs from province to province and that some patients may be required to be referred out of province to receive treatment with radiopharmaceuticals, which would increase wait times and lead to access issues. • Additionally, pERC agreed with PAG that radiopharmaceuticals would be procured by nuclear medicine programs and prepared by nuclear medicine technologists or radiopharmacists (nuclear medicine pharmacists). Radiopharmaceuticals would be administered by nuclear medicine experts in some centres and by radiation oncologists in other centres. PAG noted that administration of ^{177}Lu-Dotatate may be restricted to specialized centres that have the infrastructure to handle, prepare, and administer lutetium in a safe manner. Overall, pERC noted that a significant amount of additional resources and coordination of both nuclear medicine programs and the cancer clinics would be required to administer and monitor treatment with ^{177}Lu-Dotatate. • Patients who receive treatment with ^{177}Lu-Dotatate should also receive LAR octreotide administered intramuscularly at a dose of 30 mg approximately 24 hours after each dose of ^{177}Lu-Dotatate and then monthly after completion of all four treatments, per the NETTER-1 trial. Specifically, patients continued the four-week interval administration of octreotide LAR until disease progression.
Sequencing and Priority of Treatments • PAG is seeking information on the appropriate sequencing of somatostatin analogues and everolimus with lutetium. In addition, guidance on the appropriate treatments for patients who have progressed after treatment with ^{177}Lu-Dotatate would be helpful for implementation.	• pERC concluded that the optimal sequencing of therapies for patients with somatostatin receptor-positive midgut neuroendocrine tumours whose disease has progressed and is unresectable is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognized that provinces will need to address optimal sequencing upon implementation of a reimbursement recommendation for ^{177}Lu dotatate, and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.
Companion Diagnostic Test/Other • PAG is seeking clarity on the need for a gallium-68 scan to identify the patients with the somatostatin receptors that may respond better to ^{177}Lu-Dotatate . It is not clear what the role of the scan would be in predicting positive outcomes with the lutetium.	• pERC noted that the NETTER-1 trial used 111-In pentetreotide (OctreoScan) imaging to identify SSR positivity. Gallium Ga-68 imaging may also be an option. • pERC noted that this review and recommendation is specific to ^{177} lutetium dotatate (Lutathera). Other suppliers of lutetium products must submit to pCODR for a complete review for consideration for reimbursement.

• PAG noted that there are other suppliers of ^{177}Lu-Dotatate, in addition to the manufacturer of the lutetium product under review at pCODR. PAG identified that a review of other lutetium products would be required for funding consideration.	

PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.