CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

(Manufacturer)

Lutetium Lu 177 dotatate (Lutathera) for Gastroenteropancreatic Neuroendocrine Tumors

August 1, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Lutathera (^{177}Lu-Dotatate)_____
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Group, Clinical	Submitter_____
Organization Providing Feedback	Advanced Accelerator Applications

**The pCODR program may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☐ agrees ☒ agrees in part ☐ disagree

AAA is pleased to see pERC's acknowledgement of Lutathera's very meaningful effect on disease progression in the midgut GI-NETs population. However, the company is disappointed to see the reluctance on the part of pERC to extrapolate these benefits to a broader population of patients, which is in line with the Health Canada indication and previous health technology assessments in other jurisdictions (e.g. INESSS & NICE).

Given that the midgut population is the largest subpopulation of GI-NETs patients, it is representative of GI-NETs generally, and the results observed in NETTER-1 can reasonably be extrapolated to the broader GEP-NET population. Restriction of the use of Lutathera to only midgut GI-NETs will deny a large number of patients the opportunity to benefit from what is clearly a significant and important advancement in the treatment of GEP-NETs.

b) Please provide editorial feedback on the Initial Recommendation to aid in clarity. Is the Initial Recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder would support this Initial Recommendation proceeding to Final pERC Recommendation ("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

☐	Support conversion to Final Recommendation. Recommendation does not require reconsideration by pERC.	☒	Do not support conversion to Final Recommendation. Recommendation should be reconsidered by pERC.

If the eligible stakeholder does not support conversion to a Final Recommendation, please provide feedback on any issues not adequately addressed in the Initial Recommendation based on any information provided by the Stakeholder in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR program.

Additionally, if the eligible stakeholder supports early conversion to a Final Recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, the criteria for early conversion will be deemed to have not been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

Page Number	**Section Title**	**Paragraph, Line Number**	**Comments related to Stakeholder Information**
5	Summary of pERC Deliberations	6, line 6	"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 177Lu-Dotatate with relevant comparators is unknown".
Everolimus and sunitinib were not indicated as the standards of care at the time the NETTER-1 trial was designed, so they were not included as comparators in the clinical trial. It is for this reason that there is no direct comparative data available. In the absence of randomized controlled data for P-NET patients, a network meta-analysis could not be performed to compare Lutathera with everolimus and sunitinib. The ERASMUS study is a large, well designed, single-arm study with substantial follow-up, which included a broader progressive NET population, including P-NET patients. Patient level data from the ERASMUS trial for P-NET patients allowed a matching adjusted indirect comparison (MAIC) analysis to be performed. The MAIC analysis approach to generate comparative data, in the absence of randomized trial data, is increasingly being used in health technology assessments and the MAIC conducted for P-NET patients was requested by NICE and followed methodology outlined by their Decision Support Unit. In addition, a MAIC analysis comparing everolimus and sunitinib in P-NET patients has been previously published by Signorovitch (2013).			
4	Summary of pERC Deliberations	2, line 14	

The statement "there is uncertainty in the OS benefit of 177Lu-Dotatate given the immaturity of the data" is inconsistent with the results reported in page 8, Key efficacy results, paragraph 3, line 5:
"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 177Lu-Dotatate and control groups, respectively. An updated exploratory analysis of OS was performed based on 71 deaths; median OS was still unreached in the 177Lu-Dotatate group and was 27.4 months in the control group (HR = 0.54; 95% CI, 0.33 to 0.86)".
We suggest replacing the misleading text with the following:
"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)".

5	Summary of pERC Deliberations	2, line 8	"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 177Lu-Dotatate in the broader GEP-NETs population".

AAA would like to clarify the following points, explaining why extrapolation of the NETTER-1 results in midgut NETs patients to foregut and hindgut disease is justified:

- As sub-populations are too small to conduct controlled trials, given the orphan nature of the disease, the midgut carcinoid tumour population was selected to reduce study heterogeneity and potential bias and increase internal and external validity.
- Furthermore, the study population of patients with midgut carcinoid tumours was selected as these NETs are the most prevalent carcinoid tumour type, accounting for 40% of all types of GEP-NETs, and are therefore broadly representative of the GEP-NET population;
- Like most GEP-NETs, midgut carcinoid tumours are frequently metastatic and progressive at diagnosis, therefore, this subgroup is likely to be representative of the entire GEP-NET population;
- Midgut carcinoid tumours share pathologically important features with other GEP-NETs, such as a common cell type origin and the frequent overexpression of somatostatin receptors.

AAA has requested reimbursement according to ^{177}Lu-dotatate's Health Canada-approved indication: for all inoperable, somatostatin receptor positive GEP-NETs (including foregut, midgut, hindgut), based on the bridging of the Erasmus Phase I/II and NETTER-1 Phase III studies, in accordance with the submission strategy discussed with the EMA and the FDA.

In the Phase I-II ERASMUS trial, substantial efficacy improvement in PFS, time to disease progression and OS was achieved for GEP-NET patients receiving treatment with ^{177}Lu-dotatate. This was found to be the case in all tumour classes examined, including progressive GEP-NET, progressive P-NET, metastatic midgut NET and the broader progressive NET population comprising of bronchial, midgut, foregut, hindgut and non-functioning pancreatic. In fact, Lutathera was at least as effective in patients with P-NETs as in midgut NET patients.

The reliance on the midgut GI-NET population in the NETTER-1 trial provides greater homogeneity in the trial while also representing the single biggest class of GI-NETs. For these reasons, as well as the morphological similarity and over-expression of SSRs that creates similar vulnerability to Lutathera's mechanism of action, the reliance on NETTER-1 data as a proxy for other GEP-NETs subpopulations is reasonable.

This argument seems to have been accepted by the CGP, given their comments that *"it would be reasonable to extend treatment with 177Lu-Dotatate to other NETs, including foregut and hindgut NETs, based on the ERASMUS study and based on the rationale of mechanism of action (biological plausibility) that the clinical benefit is unlikely to differ based on anatomical site for SSR+ disease"*. In its assessment, the National Institute for health and Care Excellence relied on ERASMUS and concluded, based on the study results, that "Lutathera was clinically effective for people with GEP-NET". Despite concerns about the single arm, open-label nature of the study, NICE "acknowledged that it was the largest study of NETs currently available" (https://www.nice.org.uk/guidance/ta539/chapter/3-Committee-discussion#clinical-trial-evidence-erasmus). INESSS noted uncertainty in the estimates of comparative efficacy and safety, but chose to err on the side of access to what is undoubtedly an effective and important therapy. It is our sincerest hope that pERC will draw the same conclusions as NICE, INESSS and the many other HTA agencies who have approved Lutathera for the entire GEP-NET patients' population.			
8	Patient-reported outcomes	1, line 1	
For context, please bear in mind that QoL is improved in comparison with LAR, a treatment with some antiproliferative benefit, but which primarily controls symptoms, and is therefore expected to have a meaningful QoL benefit. Of note, the results of QLQ-C30 analyses conducted in both ERASMUS and NETTER-1 were used in the economic analysis and also showed improvements in favour of Lutathera.			
8	Patient-reported outcomes	1, line 1	Budget impact
If only midgut patients are reimbursed the budget impact would be significantly limited, as would the flexibility of AAA regarding pricing.			
2	pERC Recommendation	2	Cost-effectiveness
It is inaccurate to state that the primary analysis is subject to excessive uncertainty. Results were reported for the entire time horizon, and also for the progression-free period only. Both sets of results showed acceptable ICERs with quite limited uncertainty, and well within the bounds of conventional cost-effectiveness. Note that this analysis employed very conservative assumptions regarding utility values and costs, and is based on a regression analysis of NETTER-1 results, without use of indirect treatment comparisons.			

3 About Stakeholder Feedback

pCODR invites eligible stakeholders to provide feedback and comments on the Initial Recommendation made by the pCODR Expert Review Committee (pERC). (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, pERC makes an Initial Recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The Initial Recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation. It should be noted that the Initial Recommendation may or may not change following a review of the feedback from stakeholders.

pERC welcomes comments and feedback from all eligible stakeholders with the expectation that even the most critical feedback be delivered respectfully and with civility.

C. Application of Early Conversion

The Stakeholder Feedback document poses two key questions:

3. **Does the stakeholder agree, agree in part, or disagree with the Initial Recommendation?**

   All eligible stakeholders are requested to indicate whether they agree, agree in part or disagrees with the Initial Recommendation, and to provide a rational for their response.

   Please note that if a stakeholder agrees, agrees in part or disagrees with the Initial Recommendation, the stakeholder can still support the recommendation proceeding to a Final Recommendation (i.e. early conversion).

4. **Does the stakeholder support the recommendation proceeding to a Final Recommendation ("early conversion")?**

   An efficient review process is one of pCODR's key guiding principles. If all eligible stakeholders support the Initial Recommendation proceeding to a Final Recommendation and that the criteria for early conversion as set out in the *pCODR Procedures* are met, the Final Recommendation will be posted on the CADTH website two (2) Business Days after the end of the feedback deadline date. This is called an "early conversion" of an Initial Recommendation to a Final Recommendation.

   For stakeholders who support early conversion, please note that if there are substantive comments on any of the key quadrants of the deliberative framework (e.g., differences in the interpretation of the evidence), the criteria for early conversion will be deemed to have **not** been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting. Please note that if any one of the eligible stakeholders does not support the Initial Recommendation proceeding to a Final pERC Recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the Initial Recommendation.

D. Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents. Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the Initial Recommendation. If the feedback can be addressed editorially this will done by the pCODR staff, in consultation with the pERC chair and pERC members, and may not require reconsideration at a subsequent pERC meeting.

The Final pERC Recommendation will be made available to the participating federal, provincial and territorial ministries of health and provincial cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

4 Instructions for Providing Feedback

j) The following stakeholders are eligible to submit Feedback on the Initial Recommendation:

- The Submitter making the pCODR Submission, or the Manufacturer of the drug under review;
- Patient groups who have provided input on the drug submission;
- Registered clinician(s) who have provided input on the drug submission; and
- The Provincial Advisory Group (PAG)

k) Feedback or comments must be based on the evidence that was considered by pERC in making the Initial Recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

l) The template for providing *Stakeholder Feedback on pERC Initial Recommendation* can be downloaded from the pCODR section of the CADTH website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)

m) At this time, the template must be completed in English. The Stakeholder should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply.

n) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be provided to the pERC for their consideration.

o) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the Initial Recommendation.

p) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR program.

q) The comments must be submitted via a Microsoft Word (not PDF) document to pCODR by the posted deadline date.

r) If you have any questions about the feedback process, please e-mail pcodrsubmissions@cadth.ca

Note: CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback will be posted on the CADTH website (www.cadth.ca/pcodr). The submitted information in the feedback template will be made fully disclosable.