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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Lutetium Lu 177 dotatate (Lutathera) for Gastroenteropancreatic Neuroendocrine Tumors

August 1, 2019

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Advanced Accelerator Applications** provided three analyses:

- A primary analysis comparing Lutetium Lu 177 dotatate to octreotide long-acting release (LAR) for patients with MIDGUT-NET
- A secondary analysis comparing Lutetium Lu 177 dotatate to everolimus for patients GI-NET
- A secondary analysis comparison Lutetium Lu 177 dotatate to everolimus and sunitinib for patients with P-NET.

Table 1. Submitted Economic Model

Patient Population Modelled	*Adult patients with somatostatin receptor-positive gastroenteropancreative neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut NETs whose disease has progressed and is unresectable. For the purpose of this review, three analyses were presented:* • *MIDGUT-NET* • *GI-NET* • *P-NET*
Type of Analysis	*CUA*
Comparator – MIDGUT-NET	*Octreotide LAR*
Comparators – GI-NET	*Octreotide LAR* *Everolimus*
Comparators – P-NET	*Everolimus* *Sunitinib*
Year of costs	*2018*
Time Horizon	*20 years* • *4-week model cycle with half-cycle correction*
Discount rate	*1.5% for both costs and benefits*
Perspective	*Government*
Cost of Lutetium Lu 177	• $35,000 per dose at a dosage of 7.4 GBq (200mCi) package via intravenous injection over 30 minutes every 8 weeks for a total of $140,000 for 4 doses
Cost of Octreotide LAR 60 mg	• The list price of octreotide LAR 60 mg is $4,044.00 per dose at a dosage of 60 mg every 4 weeks via intramuscular injection.
Cost of everolimus	• 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.
Cost of sunitinib	• 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.

Model Structure	This partitioned survival model was comprised of 3 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 is unidirectional. Progression-free survival included both on treatment and off treatment.
Key Data Sources – Midgut-NET	*NETTER-1*
Key Data Sources – GI-NET	*Company submitted network meta-analysis*
Key Data Sources – P-NET	*Company submitted analysis which combined a company MAIC and a published MAIC*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparisons included for the various sub-groups of NETs are appropriate.

- Relevant issues identified included:
  - *There is net overall clinical benefit with the use of lutetium Lu dotatate for the treatment of unresectable or metastatic well-differentiated, somatostatin receptor-positive GEP-NETs in adults with progressive disease.*
  - *The NETTER-1 trial demonstrated a significant and very meaningful improvement in PFS (HR 0.21, p<0.001) with* Lutetium Lu 177 dotatate *in progressive, SSR+ well-differentiated GEP-NETs. The CGP concludes that this is compelling evidence of efficacy in a selected patient population based upon a predictive imaging biomarker*
  - *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. However, 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.*
  - *The updated, exploratory analysis of OS was performed based 71 deaths demonstrated OS was still unreached in the* Lutetium Lu 177 dotatate *group and was 27.4 months in the control group (HR=0.54, 95% CI, 0.33-0.86). The final analysis of OS is expected after 158 deaths have accrued. Of note, the additional efficacy analysis of OS was considered an administrative look at the trial data for regulatory purposes, and was not considered one of the pre-specified analyses of OS detailed in the statistical analysis plan.*
  - *The eligible patient population includes patients with well-differentiated SSR+ disease who have progressed on prior SSA therapy.*
  - *The CGP concluded that the eligible patient population from the NETTER-1 trial (midgut-NET) can be extrapolated to include foregut, hindgut primaries.*
  - *Treatment with* Lutetium Lu 177 dotatate *was well tolerated overall, though there were higher grade 3-4 adverse events compared to the octreotide LAR group.*

Summary of registered clinician input relevant to the economic analysis
pCODR did not receive input from registered clinicians.

Summary of patient input relevant to the economic analysis
Patients considered slowing or stopping disease progression, long-term disease survival tumour shrinkage and an improved quality of life and wellbeing as important to their treatment, and to treatment with Lutetium Lu 177 dotatate. Patients did note some disadvantages to treatment with lutetium including access to treatment, travel time and costs.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for lutetium Lu 177 dotatate which are relevant to the economic analysis:

- Administration of first dose is as an inpatient, followed by outpatient administration for the remaining three doses. The economic analysis accounted for an inpatient stay for the first dose.
- Appropriateness of re-treatment with Lutetium Lu 177 dotatate. Re-treatment was not considered in the economic analysis.
- Increased and different resource use for administration of radiopharmaceuticals. Additional resources may be needed to coordinate nuclear medicine physicians and medical oncologists for monitoring, including increased blood work monitoring. A blood screen every 4 weeks was accounted for in the economic model.
- Other implementation factors to consider include amino acid solutions, additional imaging and inpatient hospital admissions for the first dose. Note that no Canadian source for amino acids was available for this review. Imaging was accounted for every 12 weeks through a CT scan; inpatient hospital admissions were costed for one night.
- The gallium-68 scan to identify patients with somatostatin receptors was not included in the economic analysis from a cost perspective. The cost of scintigraphy was not included in the analysis as it was considered part of standard of care.

1.3 Submitted and EGP Reanalysis Estimates

A. MIDGUT-NET

Overall the ICER is: difficult to estimate because of uncertainty in clinical effectiveness estimates, including duration of treatment effect and long-term extrapolation from relatively short-term results.

Table 2. Submitted and EGP Reanalysis Estimates MIDGUT-NET

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	1.92	1.41	N/E
Progression-free	2.38	2.28	
Post-progression	-0.46	-0.87	
ΔE (QALY)	1.34	0.96	N/E
Progression-free	1.68	1.60	
Post-progression	-0.34	-0.64	
ΔC ($)	$100,106	0.96	N/E
ICER estimate ($/QALY)	$74,828	$87,155	

N/E: not estimable

The main assumptions and limitations with the submitted economic evaluation MIDGUT-NET are as follows:

Options provided in submitted model	The EGP was unable to explore various alternative assumptions in the submitted economic model. These include, but are not limited to: - Duration of treatment effect: CADTH guidelines state that it is not acceptable to assume the relative effectiveness of a treatment will be maintained for the duration of the intervention. Methods of exploring alternate assumptions of duration of treatment effect include treatment waning in the model and truncating the duration of effect. These were not incorporated. - Effectiveness assumptions: The submitted model extrapolated the trial data over 20 years and provided two options for parametric survival curves. In order to explore alternate hazard ratios, the submitter could have provided model options which include an option to use KM data for the observed time horizon and a parametric tail or the ability to modify the hazard ratio and change the parametric curves as necessary for best fit. Other functionality options which make exploring uncertainty easy for the EGP include exploring upper and lower confidence intervals in the economic model, and various parametric models.
Subsequent treatments	In the submitted economic model, all progressed patients received octreotide LAR 30 mg. The CGP stated that though clinical practice varies, most oncologists will stop treatment with octreotide LAR 30 mg, and many clinicians would go on to give everolimus. It was not possible to modify the proportion or type of subsequent treatments in the submitted economic model and therefore the impact of subsequent treatments on the analysis is unknown.
Source of data for background mortality	The submitter used life tables from the University of Montreal, from 1955 - 1957, to inform background mortality. No justification was provided for not using Statistics Canada life tables, with recent data. The impact of this limitation is likely minimal, however, does not align with what current life table data.
Utility values	The utility values used in the economic model were collected in the NETTER-1 trial and the ERASMUS trial. Though these values were collected alongside clinical trials, the CGP felt that they did not reflect the clinical course of these patients. According to the CGP, patients with NETs would be more likely feel worse when they progress compared to the pre-progression state. The EGP examined lower utility values in the post-progression state as a scenario analysis.

Disutility values	The disutility values used in the economic model were based on a study by Tam et al. where third parties (i.e. Treatment physicians) are used to elicit utilities. This is not the gold standard methodology for health-related quality of life as it is not a patient reported method. Further, the disutlities were much higher than those used in other pCODR economic models. For example, the disutility for fatigue used was 0.532. The EGP examined lower disutility values across the different adverse event states as a scenario analysis.
Rescue subcutaneous octreotide	In the submitted base case, it was assumed that 40% of all patients across all treatment arms were to receive rescue subcutaneous octreotide. Rescue octreotide is only given in the case of symptomatic relief and would not be needed by all patients. Functional tumors represent approximately 1/3 of patients, and the CGP stated that the assumption of 40% is much too high. The remaining 2/3 of patients have non-functional tumors and would not require rescue SC octreotide. The EGP examined lower proportions of rescue subcutaneous octreotide in scenario analyses. Though it may be expected on that lowering the proportion of patients who receive this would impact results, given that rescue octreotide is modeled as being given in equal proportions to both groups, it is not surprising that this is not a large cost driver.
Administration costs	The administration costs in the economic model were estimated at $6.71 per hour for amino acid administration at $7.37 per intramuscular injection of rescue octreotide. These administration costs were deemed to be extremely low. The EGP examined alternate, higher, administration costs to determine the impact these have on the ICUR. Administration costs are not a cost driver in the model.
Extrapolation of benefit	The median duration of follow-up of patients < 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 lutetium lu is being accrued in the extrapolated parts of the survival curves for both PFS and OS. Further, median OS was not reached in the trial. CADTH guidelines state that it is not acceptable to assume that the relative effectiveness of a treatment will be maintained for the duration of the intervention without adequate justification. In this case, the submitter has provided no justification to explain the maintenance of the expected benefit of lutetium lu over the 20-year time horizon. 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.
Probabilistic sensitivity analysis	Many of the variables included in the PSA are varied by an arbitrary factor, such 20%. Though this assumption does not affect the ICUR itself, it does affect the spread of the values when observing the cost-effectiveness scatter plot. Good modelling practice would dictate to use observed values and not an assumption of 20%.

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 re-iterated the number of limitations identified in the primary analysis of the midgut. Please see the limitations identified by the EGP above. Notably, the median duration of follow-up from the NETTER-1 trial is < 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 lutetium lu is being accrued in the extrapolated parts of the survival curves for both PFS and OS. Further, 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 restrictions in the submitted model, the EGP was unable to assess alternates in duration of treatment effect and the extrapolation of overall survival. Overall, there is uncertainty in clinical effectiveness estimates, including duration of treatment effect and long-term extrapolation from relatively short-term results.

B. GI-NET

Overall the ICER is: not estimable due to the limitations in the submitted clinical effectiveness data resulting in excessive uncertainty.

Table 3. Submitted and EGP Reanalysis Estimates GI-NET

Estimates (range/point)	Submitted Everolimus vs Octreotide	Submitted Lutathera vs Octreotide	EGP Reanalysis Everolimus vs Octreotide	EGP Reanalysis Lutathera vs Octreotide
ΔE (LY)	1.34	2.19	N/E	N/E
Progression-free	0.49	1.90		
Post-progression	0.86	0.29		
ΔE (QALY)	0.88	1.55	N/E	N/E
Progression-free	0.25	1.34		
Post-progression	0.63	0.21		
ΔC ($)	$48,234	$129,411	N/E	N/E
ICER estimate ($/QALY)	$54,811	$83,255		

N/E: not estimable

The main assumptions and limitations with the submitted economic evaluation GI-NET are as follows:

- *Comparability of trial populations:*
    - The secondary analysis for GI-NET tumors compared lutetium Lu 177 dotatate to everolimus or octreotide LAR 60 mg via network meta-analysis. This network meta-analysis made several assumptions:
    - The placebo in the RADIANT-4 trial (everolimus vs placebo) would be equivalent to the octreotide LAR arm in the NETTER-1 trial. The CGP stated that this assumption may be not be valid for PFS. In the NETTER-1 trial, PFS for octreotide was almost 10months, which is likely longer than what would be observed with placebo patients. The assumption of equivalent efficacy between placebo and octreotide LAR may not impact OS.
    - RADIANT-4 only included patients with non-functional NETs while NETTER-1 included patients with both functional and non-functional NETs. Though these patients may not be comparable, the CGP stated that it is likely that functional and non-functional patients respond to treatment in the same manner.
    - NETTER-1 only enrolled patients who were receptor positive while the receptor status for RADIANT-4 was not reported. The CGP stated that receptor positive and negative patients likely respond to treatment in the same manner.
    - The RADIANT-4 population reported results for both GI-NET and lung NETs; these results were not available separately. This pooled data was used to inform the model and may underestimate the benefit in the everolimus arm given that GI-NETs respond better to treatment than lung NETs.

C. P-NET

Overall the ICER is: not estimable due to the limitations in the methodology in the submitted clinical effectiveness data resulting in excessive uncertainty.

Table 4. ***Submitted and EGP Reanalysis Estimates P-NET***

Estimates (range/point)	Submitted Everolimus vs Sunitinib	Submitted Lutathera vs Sunitinib	EGP Reanalysis Everolimus vs Sunitinib	EGP Reanalysis Lutathera vs Sunitinib
ΔE (LY)	2.09	3.22	N/E	N/E
Progression-free	1.53	2.06		
Post-progression	0.56	1.16		
ΔE (QALY)	1.28	2.26	N/E	N/E
Progression-free	1.04	1.54		
Post-progression	0.24	0.68		
ΔC ($)	$26,708	$124,366	N/E	N/E
ICER estimate ($/QALY)	$20,866/QALY	$55,066/QALY		

N/E: not estimable

The main assumptions and limitations with the submitted economic evaluation P-NET are as follows:

- *MAIC methodology:* Combining two MAICs is not an acceptable methodology to inform all relevant outcomes in a sequential analysis. Though the submitted stated that it was necessary to use this approach in order to incorporate everolimus, other more standard methodologies exist to assess comparative effectiveness across multiple treatments and trials.
    - The EGP did not consider the results using this methodology given the limitations and uncertainty associated with an unacceptable methodology.

1.4 Detailed Highlights of the EGP Reanalysis

A. MIDGUT-NET

The EGP made the following changes to the submitted economic model:

Lower bound

- Time horizon: The submitted base case assumed a time horizon of 20 years. Based on feedback from the CGP, a 20 year time horizon was deemed too long. The CGP stated that a 10-year time horizon is more appropriate for this patient population. A 10-year time horizon aligns with previous similar CADTH reviews.
- Rescue SC octreotide: In the submitted base case, 40% of all patients received rescue SC octreotide. The CGP indicated that rescue octreotide is only given in the case of symptomatic relief and would not be needed by all patients. Functional tumors represent approximately 1/3 of patients, and the CGP stated that the assumption of 40% is much too high for this group of patients. The remaining 2/3 of patients have non-functional tumors and would not require rescue SC octreotide. The EGP, based on feedback from the CGP, assumed that 5% of *all* patients would receive SC octreotide, representing approximately 15% of those patients with functional tumors (assuming 0% of the non-functional would not receive).

Upper bound

- Not estimable given the use of post-hoc exploratory data as submitted base case clinical inputs, the uncertainty around the clinical effectiveness due to long extrapolation based on short follow-up, and the inability to explore alternatives to the duration of treatment effect.

Table 5. EGP Reanalysis Estimates

	ΔC	ΔE (LYs)	ΔE (QALYs)	ICUR	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$100,106	1.92	1.34	$74,828	--
EGP's Reanalysis for the Best Case Estimate - LOWER BOUND					
Time horizon 10 years	$86,635	1.42	0.95	$90,966	$16,138
Rescue SC octreotide 5%	$96,605	1.90	1.36	$70,902	-$3,926
Best case estimate of above 2 parameters	$83,840	1.41	0.96	$87,155	$12,327
EGP's Reanalysis for the Best Case Estimate - UPPER BOUND					
Not estimable					

B. GI-NET

- No re-analyses were undertaken.

C. P-NET

- No re-analyses were undertaken.

1.5 Evaluation of Submitted Budget Impact Analysis

A budget impact analysis for the broader GEP-NETs population was submitted. A midgut tumour specific analysis was not provided. The factors that most influence the budget impact analysis include:

- Increasing the market share uptake to 5%, 10% and 15% for years 1, 2 and 3 (from 2.5%, 4% and 6%) more than doubles the budget impact
- Removing adverse event costs from the budget impact increases the 3-year budget impact by over 40%.
- Removing the 6.10% mortality rate, increases the 3-year budget impact by ~6%.

Key limitations of the BIA model include:

- An underestimation of the market share. The CGP indicated that in Manitoba alone, they send approximately 100 patients out of province to be treated with Lutetium Lu 177 dotatate.

1.6 Conclusions

A. MIDGUT-NETs

The EGP's best estimate of ΔC and ΔE for lutetium Lu 177 dotatate **when compared to octreotide is:**

- Between $87,155/QALY and not estimable
- It is difficult to estimate where the best estimate for this comparison would lie. Several limitations were present in the clinical effectiveness data, including use post-hoc exploratory analyses and the inability to examine alternate duration of treatment effects.
- The extra cost of lutetium Lu 177 dotatate is at least $83,840 (ΔC). *The main factors that most influence ΔC include the administration costs and the time horizon.*
- The extra clinical effect of lutetium Lu 177 dotatate is at least 0.96 (ΔE). *The main factors that influence ΔE include the time horizon and utilities post-progression.*

B. GI-NETs

The EGP did not provide a best estimate for the GI-NET sub-group due to several assumptions made in conducting the NMA notably that octreotide LAR was clinically equivalent to the placebo arm of the RADIANT-4 trial, and that the treatment effect of everolimus did not differ by receptor status. There was substantial heterogeneity in the included studies and patient characteristics among the included studies. Further, Lutetium Lu 177 dotatate did not demonstrate any statistically significant differences compared to everolimus, octreotide LAR or placebo. It was therefore not possible to either do re-analyses or provide a best estimate for GI-NETs.

C. P-NETs

The EGP did not provide a best estimate for the P-NET sub-group due to the methodological limitations and assumptions around the clinical effectiveness estimates. Notably, the submitter combined MAICs in order to provide all necessary clinical effectiveness data to inform the sequential analysis. Combining MAICs is not an acceptable methodology. It was therefore not possible to either do re-analyses or provide a best estimate for P-NET.

Overall conclusions of the submitted MIDGUT-NET model:

- *The general model structure provided for the MIDGUT-NET primary analysis was basic. The model inputs were limited, and the EGP was restricted in its ability to conduct scenario analyses.*
- *Due to these restrictions, the EGP was unable to assess alternates in duration of treatment effect and the extrapolation of overall survival.*
- *Further, a post-hoc exploratory analysis was used to inform the clinical effectiveness assumptions.*

- *Given the limitations associated with the NETTER-1 trial, evaluating alternative clinical effectiveness assumptions would have been informative.*
- *Results should be interpreted with caution.*

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Gastrointestinal Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of Lutetium Lu 177 dotatate (Lutathera) for (GEP-NETs). A full assessment of the clinical evidence of Lutetium Lu 177 dotatate (Lutathera) for (GEP-NETs) is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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