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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Everolimus (Afinitor) for Neuroendocrine Tumours of Gastrointestinal or Lung Origin

December 1, 2016

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TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Novartis Pharmaceuticals Canada Inc. compared everolimus plus best supportive care to best supportive care alone for patients with advanced (unresectable or metastatic), progressive non-functional gastrointestinal or lung neuroendocrine tumours; based on efficacy data from the RADIANT-4 trial. The Submitter is requesting listing as per the Health Canada indication.

Table 1 Submitted Economic Model

For the treatment of unresectable, locally advanced or metastatic, well-differentiated, non-functional neuroendocrine tumors (NETs) of gastrointestinal or lung origin in adults with progressive disease	*Modelled population as per Radiant-4 trial.*
Type of Analysis	*Cost Utility Analysis and Cost Effectiveness Analysis*
Type of Model	*Partitioned-survival analysis with three health states (stable disease, disease progression, death).* *Tunnel states were included for adverse events.*
Comparator	*Best supportive care (BSC), reported as dexamethasone, prednisone and nutritionist visits*
Year of Costs	*2016*
Time Horizon	*10 years (base case)*
Perspective	*Canadian public payer*
Cost of Everolimus	*Everolimus costs $200.0850 per 10 mg tablet. At the recommended dose of 10mg daily, everolimus costs:* • *$200.0850 per day* • *$5,602.38 per 28-day course*
Model Structure	*The partitioned survival model was comprised of three health states: stable disease, disease progression, death. Kaplan-Meier curves from the trial were used, after which derived parametric curves were used to extrapolate response.* *See **Error! Reference source not found.** in Section 2.1 of the Technical Report*
Key Data Sources	*Efficacy data were sourced from one randomised, phase 3, double-blind, placebo-controlled trial of adults (aged ≥18 years) with advanced, progressive, well-differentiated, non-functional neuroendocrine tumours of lung or gastrointestinal origin (RADIANT-4).* *Utility values were based on a mapping study of data from the FACT-G quality of life questionnaire to the EQ-5D using an algorithm developed in the UK.* *Resource use was based on expert opinion* *Cost information was sourced from UK and Canadian sources.*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of everolimus to best supportive care (BSC) is appropriate.

- Relevant issues identified included:
  - The CGP considered somatostatin analogues (SSAs; e.g. octreotide, lanreotide) to be a relevant comparator. There was one ongoing trial identified (Section 6.4 of the Clinical Guidance Report) that evaluates pasireotide LAR, everolimus alone, and pasireotide LAR + everolimus combination in adult patients with advanced (unresectable or metastatic) neuroendocrine carcinoma (typical and atypical) of the lung and thymus; however, as the trial is ongoing results are not yet available. The CGP identified 1 RCT comparing placebo to octreotide (PROMID), and although an indirect treatment comparison was considered, the study populations in PROMID and RADIANT-4 are heterogeneous and preclude an indirect comparison (Section 8 of the Clinical Guidance Report). The Submitter did not present a comparison of everolimus with SSAs as part of their economic submission.
  - In the RADIANT-4 trial, prior SSA use was 54% and was similar between groups.

Summary of Registered Clinician input relevant to the economic analysis

None provided for this submission.

Summary of patient input relevant to the economic analysis

Patients and caregivers considered the following factors to be important to consider for the review of everolimus: improvement in quality of life, tumour shrinkage, slow disease progression, improvement in symptoms, clear information on the side-effect profile, and easier access to more treatment options.

- The economic model submitted by the manufacturer takes into account quality of life, progression free survival and overall survival as well as adverse events. Tumour shrinkage was not reported directly as part of the economic model.
- As per pCODR guidelines, the perspective of the model was that of the publicly funded healthcare system and did not consider patient or caregiver time costs.

EGP noted that the feedback received was not solely from Canadians, as the survey used to obtain information was distributed to respondents outside of Canada.

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 everolimus for the submitted indication which are relevant to the economic analysis:

- PAG noted there is uncertainty regarding the most appropriate comparator as there is no standard "standard of care" for treating patients with gastrointestinal or lung NETs; it may include treatment with somatostatin analogues (SSAs), chemotherapy, or best supportive care. The Submitter's economic analysis only considered chemotherapy and SSAs in patients with progressive disease.
- There is an unmet need in patients with NETs of gastrointestinal or lung origin whose disease has progressed or relapsed.
- PAG noted that while RADIANT-4 included both previously treated patients and treatment naïve patients, patients who had received more than one line of prior chemotherapy or treatment with an mTOR inhibitor were excluded, and seeks clarity on the appropriate patient population to treat.
- PAG is seeking information on the use of everolimus after treatment failure with SSAs. This specific subgroup comparison was not provided in the submitted economic analysis. However, it was noted that in the trial, 53% of patients in the everolimus group, has

previous treatment with SSA. In subgroup analysis, both patients previous treated with SSAs (HR 0.52 95% CI (0.34 to 0.81)) and those not previously treated (HR 0.60 95% CI (0.30 to 0.94)) showed significant improvement in PFS over placebo treatment.

- The availability of multiple doses is an enabler to implementation. However, as there are different strengths, PAG is concerned that there may be dose wastage when patients change doses prior to completing the pack of the previous strength. The economic model assumed all patients would receive the 10 mg tablet of everolimus.
- PAG indicated that the flat pricing structure is a barrier to implementation. The EGP notes that the flat pricing is only for Alberta, Saskatchewan and Quebec. Of note, a 7.5 mg tablet is available. In other provinces, there is a slightly lower price for the 7.5 mg tablet; however this is based on a 30 day supply for the 7.5 mg as opposed to a 28 day supply for all other strengths. The submitter provided feedback on pERC's initial recommendation and noted that PAG discussed the flat pricing structure of the 2.5mg, 5mg and 10mg tablets. The submitter also stated that the 7.5 mg tablet does not have the same price as the other tablets in most provinces. The EGP would like to note that the submitter tested the cost of everolimus in one-way sensitivity analyses (including a lower cost than for the 7.5 mg tablet) which indicated that the slightly lower cost of the 7.5 mg tablet will not have a substantial impact on the cost-effectiveness of everolimus.
- Although the patient population is expected to be small, the cost of treatment is high and the duration of treatment is unknown, thus there may be an incremental budget impact.

1.3 Submitted and EGP Reanalysis Estimates

The main cost driver in the Submitter's model was the cost of everolimus over the time horizon and the progression-free survival estimates used. The driver of the clinical impact was the overall survival estimates (based on parametric distributions). The clinical inputs were derived from a randomised, double-blind, placebo-controlled, phase 3 trial of adult patients (aged ≥18 years) with advanced, progressive, well-differentiated, non-functional neuroendocrine tumours (NETs) of lung or gastrointestinal origin (RADIANT-4). The Submitter used trial data from the RADIANT-4 study to generate Kaplan-Meier (K-M) life tables. Parametric distributions were derived and tested for best fit to the trial data (based on AIC, BIC and visual fit). The EGP noted that 79% of the QALY benefit seen in the Submitter's model occurred when using the extrapolated clinical data.

Table 2 Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis	EGP exploratory analysis
ΔE (LY)	0.823	0.540	0.498
Progression-free	0.373	0.364	0.364
Post-progression	0.450	0.175	0.134
ΔE (QALY)	0.616	0.411	0.381
Progression-free	0.290	0.284	0.284
Post-progression	0.326	0.127	0.097
ΔC ($)	$96,098	$95,569	$94,934
ICER estimate ($/QALY)	$155,895	$232,565	$249,486

Δ = difference; EGP = Economic Guidance Panel; LY = life-year; QALY = quality-adjusted life-year

The main assumptions and limitations, in no order of importance, with the submitted economic evaluation were:

- **The Submitter did not consider somatostatin analogues (SSAs) as an appropriate comparator.** Feedback from the CGP suggested SSAs are an appropriate comparator, but

SSAs such as octreotide and lanreotide were not considered by the Submitter in their submitted economic analysis.

- **Trial-based PFS Kaplan-Meier curve may have overestimated benefit.** Trial data for PFS were used for the first 26 months in the model as K-M curves, after which parametric distributions derived from the trial data were applied to extrapolate the data to a 10 year time horizon. The EGP noted that after 22 months the K-M curve for everolimus flattened out to month 26, indicating that no patients appeared to progress over this time (a similar trend was seen for BSC). Feedback from the CGP suggested this continuation of benefit was unlikely. Additionally, the number of patients at risk at 26 months is very small in both groups due to censoring; by shortening the duration of the trial-based PFS data to 22 months, this bases the results on a more reasonable number of people (more reliable information) and thus is a reasonable reanalysis to address the uncertainty with the data.
- **OS benefit prediction for everolimus compared to BSC is associated with uncertainty.** Trial data were used for the first for the first 27 months in the model, after which a parametric curve derived from the trial data (via Kaplan-Meier curve) was applied to everolimus to extrapolate the data to a 10 year time horizon. The duration of trial data differed slightly to PFS as there were two data cut-offs for the RADIANT-4 trial. A hazard ratio was applied to BSC to determine the BSC relative to the everolimus curve. The hazard ratio was applied based on an analysis of the data in November 2015 (HR = 0.73, 95% CI: 0.48 to 1.11). The initial analysis undertaken in November 2014 suggested a more pronounced (though non-significant) benefit (HR = 0.64, 95% CI: 0.40 to 1.05), suggesting a trend toward a weak or no overall survival benefit. Feedback from the CGP suggested testing a variety of hazard ratios was appropriate based on the uncertainty of the overall survival benefit based on the RADIANT-4 trial. Although the EGP Reanalysis is based on the OS hazard ratio from the November 2015 cut-off, as these data are not mature, there is a trend towards reduced effect over time, and at both timepoints the upper bound crossed 1, The EGP undertook an exploratory analysis to test a higher OS hazard ratio based on the trend towards reduced effect over time (0.80). Once the data set reaches maturity, the final OS hazard ratio should be given consideration by decision makers, as this parameter was found to have a notable impact on the cost-effectiveness of everolimus.
- **The parametric distribution used to model OS did not accurately represent the trajectory of disease.** The Submitter determined that a Weibull distribution best represented the estimated long-term survival benefit of patients with gastrointestinal and lung NETs, despite the gamma distribution fitting based on AIC and BIC (the Submitter reported that there was low precision in the parameter estimates as justification for not using this curve). Feedback from the CGP indicated that the gamma curve was more likely to represent the overall survival trajectory of patients than the Weibull distribution used by the Submitter. The EGP noted that the distributions were influenced by an extended period on the K-M curve during which no events occurred until the trial data were censored, which may have impacted the shape and scale of the distributions.
- **A 10-year time horizon may overestimate the expected patient lifetime.** Feedback from the CGP suggested that a time horizon of 10 years may be too long; however given the revisions made to the clinical assumptions in the model, unless the time horizon is limited to less than 5 years, the time horizon has little impact on the ICUR.
- **The modelling of utility values does not accurately represent patients with NETs.** The Submitter derived health state utility values from a mapping algorithm for stable disease and progressive disease that were applied constantly throughout the model. Feedback from the CGP suggested that although the utility values appear to generally represent the stable disease and progressive disease health states, quality of life was not constant for patients with NETs and the model structure did not take into account events that could occur that impact quality of life while in the stable disease or progressive disease health states. EGP was unable to test the impact of time dependent utility values.

- **The resource use and associated costs were overestimated for BSC compared to everolimus.** Feedback from the CGP suggested that several of the resource use assumptions may overestimate the costs associated with BSC. CGP suggested two assumptions were unlikely to be appropriate: the assumption that BSC patients with stable disease had eight times as many emergency room visits, and twice as many hospitalisations was unlikely to be appropriate as any perceived additional visits due to disease for BSC would be lessened by additional visits for everolimus toxicity, and the assumption that patients would receive everolimus in the post-progression health state should not differ between treatment group and continued treatment with everolimus was not expected to occur in clinical practice. However, in general this did not impact the ICUR results in a substantial manner.

1.4 Detailed Highlights of the EGP Reanalysis

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

- **Trial-based PFS data used to month 22.** The censoring with the clinical trial data meant that there were long tails on the K-M curves for both BSC and everolimus, which are not expected in clinical practice and are associated with uncertainty. As the values were unchanged from month 22 through month 26 for everolimus, given censoring and small numbers, the EGP undertook a reanalysis using trial data up to month 22 for both treatments.
- **The distribution for OS was revised from Weibull to Gamma.** Feedback from the CGP suggested that the gamma distribution for OS was more representative of patient trajectory than the Weibull distribution for OS. This was applied to both treatments.
- **The OS hazard ratio was revised using both higher and lower values.** The EGP noted the OS hazard ratios at the November 2014 and November 2015 cut-offs are not statistically significant, and the apparent decline in survival benefit for everolimus over time. The submitter provided feedback on pERC's initial recommendation and stated that they disagreed with the EGP's choice of hazard ratio of overall survival for the EGP's best case estimate. The submitter felt that the hazard ratio estimates from the RADIANT-4 trial were more appropriate. Upon reconsideration, the EGP recognized the merits of using published values as opposed to speculating on data trends and therefore, the EGP undertook reanalyses testing hazard ratios based on the November 2014 data cut-off hazard ratio (0.64), and the 95% confidence intervals (95% CIs) around the hazard ratio November 2015 data cut-off (0.48 and 1.11). However, to assess the uncertainty associated with the manufacturer's OS hazard ratios based on the trend for a continued decline in effect, the EGP undertook an exploratory analysis using a hazard ratio that continues the trend in reduced effect (0.80). The EGP base case reanalysis was undertaken using the submitter's base case OS hazard ratio; 0.73. The EGP also tested the upper and lower estimates (95% CIs) around the OS hazard ratio, which was the basis for the Upper and Lower bounds of the EGP's best estimate. The EGP also undertook an exploratory analysis inferring that the hazard ratio will continue to decline at the final timepoint, based on the available data.
- **Remove the half-cycle correction applied to the cost of everolimus.** Everolimus is supplied in 28- or 30-day packs, received at the start of the first 30-day model cycle. Thus, the cost would be borne up front, not half-way through the cycle. EGP undertook a reanalysis excluding the half-cycle correction as applied to the cost of everolimus.
- **Resource use for hospitalisation and ER visits for patients with stable disease were revised for BSC to be equivalent to everolimus.** Feedback from the CGP suggested that the assumption by the Submitter regarding the proportion of hospitalisations and ER visits by patients with stable disease overestimated the proportion of events for

patients who are not being treated with everolimus. EGP undertook a reanalysis using the Submitter's rates for everolimus for both the everolimus arm and BSC arm.

- **Assumed use of everolimus in post-progression is not appropriate.** Feedback from the CGP suggested that everolimus is unlikely to be used in patients who progress while on treatment, which is supported by text in the product monograph. EGP undertook a reanalysis assuming no use of everolimus in post-progression for either treatment group.

Table 3 Detailed Description of EGP Reanalysis

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Submitter's best estimate	**$96,098**	**0.616**	**0.823**	**$155,895**	--
ONE-WAY REANALYSES					
Gamma distribution used for OS	$92,078	0.411	0.540	$223,809	+$67,914
Trial-based data applied for 22 cycles after which the parametric distributions were used.	$91,832	0.616	0.823	$149,088	-$6,087
Revised OS hazard ratios tested					
0.48	$101,316	0.868	1.170	$116,665	-$39,230
0.64	$97,845	0.701	0.939	$139,565	-$16,330
0.80 (exploratory)	$94,835	0.555	0.738	$170,866	+$14,971
1.11	$90,112	0.324	0.419	$278,093	+$122,198
Half-cycle correction not applied to cost of everolimus	$99,224	0.616	0.823	$160,966	+$5,071
Rates of hospitalisation and ER visits were assumed the same for everolimus and BSC in patients in stable disease	$99,245	0.616	0.823	$161,000	+$5,105
No use of everolimus in post-progression for either treatment arm	$97,757	0.616	0.823	$158,587	+$2,692
EGP BEST ESTIMATE					
EGP best estimate All of the above, using OS HR of 0.73	**$95,569**	**0.411**	**0.540**	**$232,565**	**+$76,670**
EGP BEST ESTIMATE (LOWER BOUND)					
All of the above, using an OS HR of 0.48	$98,350	0.544	0.724	$180,711	+24,816
EGP BEST ESTIMATE (UPPER BOUND)					
All of the above, using an OS HR of 1.11	$92,629	0.270	0.345	$342,867	+186,972
EGP EXPLORATORY ANALYSIS					
EGP best estimate All of the above, using OS HR of 0.80	**$94,934**	**0.381**	**0.498**	**$249,486**	**+$93,591**

Δ = difference; BSC = best supportive care; EGP = Economic Guidance Panel; ER = Emergency Room; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; QALY = quality-adjusted life-year.

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the additional cost of drug for everolimus, the prevalence of GI/lung NETs in Canada, assumptions around market share and constant uptake of the drug.

Key limitations of the BIA model include:

- The assumptions that more than half of patients with non-functional, advanced, progressive GI or lung NETs would be reimbursed (eligible), and approximately half of those eligible will receive everolimus suggest the Submitter underestimated the proportion of patients that will receive everolimus. One-way analyses suggest assuming 100% reimbursement or 75% uptake of everolimus would increase the baseline budget impact estimates by 50% or more.
- Feedback from the CGP suggested rate of uptake is unlikely to be constant, as the majority of eligible patients will receive treatment in Year 1, followed by lower rates in subsequent years based on disease progression while on treatment. Given the model structure, this was unable to be tested.
- The annual cost of everolimus may been underestimated based on 327 days of use per year at a dose intensity of 79%, particularly as the analysis doesn't account for the potential for dose reductions (67% in RADIANT-4). As everolimus is supplied as 28-day and 30-day packs, the timing of any dose reduction will impact the BIA. Assuming 100% dose intensity and 365 days of use for everolimus increased the baseline budget impact estimates by 40%.
- The prevalence of patients with neuroendocrine tumours in Ontario is uncertain, as the Submitter's model is based on US data which reported ~3.5 per 100,000 and was assumed to remain constant over time. Feedback from the CGP suggested that the incidence of GI and lung NETs increased annually in Ontario from 1994 to 2009 to 5.86 per 100,000, and that the prevalence of the disease in the Canadian population has continued to increase.[1] EGP tested a prevalence of 0.05% per year which increased the baseline budget impact estimates by more than 40%.
- The Submitter's BIA did not include a reference case. As SSAs were deemed a relevant comparator, everolimus may displace some SSA use. However, as the annual drug cost of everolimus ($73,000) is approximately three times that of lanreotide ($18,000 to $27,000).

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for everolimus when compared to BSC is:

- $232,565 based on the assumption that the OS hazard rate from the November cut-off is appropriate. The EGP tested the upper and lower estimates around this hazard rate which indicated the ICUR ranged from $180,711/QALY to $342,867/QALY. However, when the upper estimate was applied to the model, the results indicated that everolimus patients would achieve worse effect in the post-progression period than patients receiving BSC, thus the Upper and Lower bound results should be viewed with caution. The EGP also undertook an exploratory analysis with a revised OS hazard rate based on inference from the reduced effect over time from the two data cut-offs, which indicated the ICUR may be slightly higher than the EGP's best estimate: $249,486/QALY**.** As was noted in the CGR, the CGP indicated there was a clinical benefit associated with everolimus; however, the EGP expressed concern regarding magnitude of the benefit given the uncertainty around the overall survival benefit. Once the RADIANT-4 study OS data set reaches maturity, the final OS hazard ratio should be given consideration by decision makers, as this parameter was found to have a notable impact on the cost-effectiveness of everolimus.
- The extra cost of everolimus is between $90,112 and $101,316. The incremental cost of everolimus is relatively stable; it is predominantly impacted by the hazard ratio for overall survival and rate of hospitalisation and ER visits.

- The extra clinical effect of everolimus is between 0.270 QALYs and 0.868 QALYs (ΔE). The magnitude of clinical benefit is influenced by the hazard ratio for overall survival, and the parametric distribution applied post-trial.

Overall conclusions of the submitted model:

- The model is designed similarly to previously published models for pancreatic NETs; however, there was no evidence of model validation provided by the Submitter.
- There is some uncertainty regarding the magnitude of the benefit for everolimus based on the data from the RADIANT-4 trial.
- The EGP best estimate is driven by revised clinical assumptions, primarily impacted by the overall survival assumptions in the post-trial period.
- Future research should provide additional details regarding: the magnitude of the benefit associated with everolimus, particularly as to whether there is an overall survival benefit; the comparative effectiveness of everolimus compared to SSAs; drug wastage; and treatment patterns following progression.

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 Endocrine 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 everolimus for the treatment of unresectable, locally advanced or metastatic, well differentiated non-functional neuroendocrine tumours (NETs) of gastrointestinal or lung origin in adults with progressive disease. A full assessment of the clinical evidence of [drug name and indication] 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. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

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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