pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL 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.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with the *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Everolimus (Afinitor)

Submitted Funding Request:
For the treatment of unresectable, locally advanced or metastatic, well-differentiated non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease

Submitted By:
Novartis Pharmaceuticals Canada Inc.

Manufactured By:
Novartis Pharmaceuticals Canada Inc.

NOC Date:
May 17, 2016

Submission Date:
May 30, 2016

Initial Recommendation Issued:
September 29, 2016

pERC RECOMMENDATION

pERC recommends reimbursement of everolimus (Afinitor) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of unresectable, locally advanced or metastatic, well-differentiated non-functional neuroendocrine tumours (NETs) of gastrointestinal or lung origin (GIL) in adults with documented disease progression within six months and with a good performance status. Treatment should continue until confirmed disease progression or unacceptable toxicity.

The Committee made this recommendation because it was satisfied that there is a net clinical benefit of everolimus based on the magnitude of the observed difference in progression-free survival (PFS) between everolimus and placebo, despite recognizing its moderate toxicities. pERC concluded that everolimus aligned with patient values. However, the Committee concluded that everolimus could not be considered cost-effective at the submitted price and the pCODR Economic Guidance Panel's (EGP's) estimates of the range of incremental cost-effectiveness ratio (ICER).

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC was satisfied that there is a net clinical benefit with everolimus, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of everolimus to an acceptable level.

Generalizability of Results to Patients with More Than One Line of Prior Chemotherapy
pERC noted that the majority of patients with unresectable, locally advanced, or metastatic, well-differentiated non-functional NETs GIL would receive only one line of chemotherapy, except in uncommon

situations, such as during participation in a clinical trial. pERC felt that, in such patients, the clinical benefit of everolimus would be similar to that observed in the pivotal trial (RADIANT-4). Furthermore, pERC was of the opinion that the toxicity in this subgroup of patients would not be increased and that the size of this potential subgroup would be very small. Therefore, the Committee agreed that it would be reasonable for jurisdictions to consider reimbursing everolimus in this subgroup of patients.

Collecting Evidence to Inform Effectiveness and Cost-Effectiveness
Jurisdictions that have evidence-gathering systems in place may want to consider collecting additional effectiveness data on everolimus use for NETs GIL. These data could contribute to providing clarity on the magnitude of benefit observed with everolimus and better inform real-world cost-effectiveness estimates of everolimus in the treatment of NETs GIL.

SUMMARY OF pERC DELIBERATIONS

NETs are a heterogeneous group of cancers arising from a variety of anatomic sites with approximately 50% being of gastrointestinal (GI) and 25% being of lung origin. The incidence of NETs has been steadily increasing over the past four decades, although the overall incidence of metastatic NETs appears to have remained stable. Although well-differentiated NETs often have relatively indolent biology, the 10-year overall survival is about 50% and the prevalence of the disease in the Canadian population has continued to increase.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

NETs are classified "non-functional" in the absence of either clinical symptoms due to hypersecretion of hormones or bioactive amines. An estimated 50% of GI NETs and 90% of lung NETs are non-functional. Non-functional NETs may cause symptoms due to progressive local-regional disease and result in abdominal pain, intermittent or complete intestinal obstruction, intestinal ischemia, ascites, and constitutional symptoms secondary to bulky hepatic metastases. There is no current standard of care for the treatment of non-functional NETs GIL. Patients may be treated with best supportive care (BSC), somatostatin analogues (SSAs), or chemotherapy. However, cytotoxic chemotherapy is seldom considered due to the conflicting nature of evidence documenting effectiveness and also potential detrimental impacts on quality of life. Therefore, the Committee agreed there is a need for alternative treatment options that are effective, and without detrimental impact on patients' quality of life.

pERC deliberated upon the results of a phase 3, randomized, double-blind, placebo-controlled study (RADIANT-4), comparing everolimus (10 mg orally per day) plus BSC (n = 205) to placebo plus BSC (n = 97). The Committee noted a large PFS benefit of everolimus compared with placebo. pERC also noted the trend in overall survival (OS); however, it recognized that data were based on two pre-planned interim analyses and, therefore, pERC concluded that there is uncertainty in the OS benefit given the immaturity of the data. The Committee also noted that there was no worsening in quality of life in the RADIANT-4 trial.

pERC also considered the safety of everolimus and noted that the moderate toxicities were consistent with those seen in other tumour types. As a result, the Committee noted the potential for the unintentional unblinding of patients and clinicians in the trial, given the well-known adverse event profile of everolimus and, thus, the potential for bias. pERC also recognized the Clinical Guidance Panel's (CGP's) concerns regarding pneumonitis and infections, which occur in a minority of patients and are usually non-fatal. Overall, the Committee concluded that toxicities were moderate, but manageable.

The Committee noted that RADIANT-4 was restricted to patients with a World Health Organization (WHO) performance score of 0 or 1 and specifically excluded patients with a WHO performance score of ≥ 2. Notwithstanding the CGP's rationale for limiting to patients with a WHO performance score of 0 or 1 (i.e., no evidence for patients with WHO performance score of ≥ 2 in the RADIANT-4 trial), the Committee concluded that it is reasonable to make this treatment available to patients with a good performance status.

The Committee deliberated upon input from one patient advocacy group concerning everolimus and noted that disease control and additional treatment options were most important to patients. pERC agreed that everolimus offers another treatment option, with PFS benefits, and has a well-understood toxicity profile. pERC also acknowledged that patients expressed a need to be provided with a full description of the potential side effects of treatment, because patients wanted to be able to make informed decisions about their treatment plan. This reinforces the recognized need for jurisdictions and tumour groups to include all side effects related to everolimus in their information packages for everolimus. Overall, pERC concluded that everolimus aligned with patient values.

pERC deliberated upon the cost-effectiveness of everolimus and concluded that, at the submitted price, it is not cost-effective compared with BSC. pERC considered estimates provided by the submitter and reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP) and noted the uncertainty regarding the OS benefit, given the immature survival data. The factors that most influence the incremental cost include rates of hospitalization and emergency room (ER) visits and half-cycle corrections were not applied to cost of everolimus; however, pERC noted that the incremental cost was only slightly impacted by these factors. pERC also noted that the cost of everolimus was a driver of the incremental cost. The factors that most influence the incremental effectiveness include the hazard ratio for OS and the parametric distribution applied post-trial. The Committee also noted the overestimation of the trial-based PFS Kaplan–Meier curve in the submitter's model and agreed with the EGP's reanalysis. pERC discussed the use of a 15-year time horizon; however, it was confirmed by the EGP that using a 15-year time horizon as opposed to a 10-year time horizon would have no impact on the ICER. Overall, pERC noted that the uncertainty in the ICER was due largely to the uncertainty in the extrapolated OS benefit and in the comparative OS benefit of everolimus compared with BSC.

The Committee also considered factors affecting the feasibility of implementing a positive funding recommendation for everolimus for the treatment of unresectable, locally advanced or metastatic, well-differentiated non-functional NETs GIL in adults with progressive disease. The Committee recognized and agreed with pCODR's Provincial Advisory Group (PAG) that there would be a small incremental budget impact due to the small number of patients; however, the treatment cost per patient is high and the duration of treatment is unknown. pERC noted that the factors that most influence the budget impact analysis include the additional cost of everolimus, the prevalence of NETs GIL in Canada, assumptions regarding the market share, and constant uptake of the drug. The Committee agreed that the submitted budget impact analysis may have underestimated both utilization and dose adjustments, and noted the uncertainty related to the prevalence of patients with NETs in Ontario. pERC also agreed with PAG that the flat pricing structure (for 2.5 mg, 5 mg, and 10 mg tablets) is a barrier to implementation. pERC acknowledged PAG's concerns with wastage (i.e., when dose adjustments are made and a different tablet strength is required prior to the patient completing the strength initially provided).

pERC noted PAG's request for information on the use of everolimus after failure of treatment with SSAs. The Committee agreed with the Clinical Guidance Panel (CGP), based on the subgroup analysis results, that everolimus was effective in patients who failed an SSA and in SSA-naive patients. pERC also discussed PAG's request for clarity on the use of everolimus in patients who have received more than one line of prior chemotherapy. Given the conflicting evidence documenting the effectiveness of chemotherapy and the potential unfavourable impacts on quality of life, pERC noted that it is unlikely that patients would be treated with more than one line of prior chemotherapy. Notwithstanding the CGP's justification to exclude patients with more than one line of prior chemotherapy (i.e., given the lack of evidence to support its use in this group), pERC believed that, if everolimus were made available to this subgroup of patients, toxicity should not be more and benefits should not be less than those observed in RADIANT-4. Therefore, the Committee agreed that it would not consider more than one line of systemic therapy to be a barrier to treatment.

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 pCODR clinical and economic review panels, Input from one patient advocacy group (Carcinoid Neuroendocrine Tumour Society of Canada [CNETS Canada])and Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of everolimus compared with best supportive care (BSC) for the treatment of unresectable, locally advanced or metastatic, well-differentiated, non-functional neuroendocrine tumours (NETs) of gastrointestinal or lung (GIL) origin in adults with progressive disease.

Studies included: phase 3, randomized, double-blind, placebo-controlled study

The pCODR systematic review included RADIANT-4, a phase 3, randomized (2:1, intervention:control), double-blind, placebo-controlled study. There were 302 patients randomized to everolimus (10 mg orally per day) plus BSC (n = 205) or placebo plus BSC (n = 97). Randomization was stratified by previous somatostatin analogue (SSA) treatment, tumour origin, and World Health Organization (WHO) performance status. Key inclusion criteria included adults aged 18 years or older, with pathologically confirmed advanced (unresectable or metastatic) non-functional well-differentiated NET GIL, WHO performance score 0 or 1, and documented radiological disease progression within six months. The Committee noted that patients previously treated with an SSA were eligible if disease progression were documented during or after last treatment, and that patients with more than one line of chemotherapy were excluded. The study was conducted in 25 countries, including Canada (with 18 Canadian patients across seven sites). The primary outcome of the trial was progression-free survival (PFS); secondary outcomes included overall survival (OS), objective response rate, disease control rate, health-related quality of life (HRQoL), WHO performance status, and safety. Novartis Pharmaceuticals Corporation funded the study.

The pCODR review also provided contextual information, in the form of comparison with other literature and a relevant ongoing trial.

Patient populations: Similar baseline characteristics, more than half with prior somatostatin analogue treatment

Baseline characteristics between the two treatment groups were similar, with a few differences: patients were older in the everolimus group (median age: 65 versus 60), there was a greater percentage of female patients in the everolimus group (57% versus 45%), and more patients in the placebo group were previously treated with surgery (59% versus 72%). More than half of all patients had received a prior SSA.

Key efficacy results: Clinically meaningful progression-free survival, immature survival data

The key efficacy outcome deliberated on by pERC PFS, OS, and response.

The median PFS, as assessed by central review, was 11.0 months (95% confidence interval [CI], 9.2 to 13.3) in the everolimus group and 3.9 months (95% CI, 3.6 to 7.4) in the placebo group (November 2014 data cut-off). Everolimus was associated with a 52% reduction in the estimated risk of disease progression or death (hazard ratio [HR], 0.48; 95% CI, 0.35 to 0.67; $P < 0.00001$; final analysis). The estimated PFS at 12 months, as assessed by central review, was 44% in the everolimus group and 28% in the placebo group. Investigator-assessed PFS findings were consistent with central review and treatment effect–related PFS appeared to be consistent across all subgroups (including after failure of SSA, WHO performance score 1, and liver burden).

As the PFS results were significant, a planned interim analysis for OS was done after a total of 70 deaths (37% of the total targeted 191 deaths for the final OS analysis) at the November 28, 2014 data cut-off; a

36% reduction in the estimated risk of death relative to placebo was found, although statistical significance was not attained (HR, 0.64; 95% CI, 0.40 to 1.05). The estimates of OS at the 25th percentile (25% of patients having survival events) were 23.7 months (95% CI, 17.6 to 27.3) in the everolimus group and 16.5 months (95% CI, 9.0 to 21.0) in the placebo group. Data were not mature enough to provide an estimation on median OS.

A pre-planned secondary interim OS analysis was done based on 101 deaths (53% of the targeted 191 deaths): 66 (32%) in the everolimus group and 35 (36%) in the placebo group (November 30, 2015 data cut-off). Median duration of study follow-up was 33.4 months. Everolimus was associated with a 27% reduction in the estimated risk of death compared with placebo, although statistical significance was not attained (HR = 0.73; 95% CI, 0.48 to 1.11; *P* = 0.071). Crossover was not permitted until after the primary analysis if improvement in PFS was statistically significant. Final OS analysis will be performed after a total of 191 deaths.

Confirmed objective responses (by central radiology review; all partial response) were recorded in four (2%) patients receiving everolimus and in one (1%) receiving placebo. Minor responses in target lesions were observed in 64% of everolimus-treated patients compared with 26% of those receiving placebo. Disease control rates were observed in 82% of patients in the everolimus group and 65% of patients in the placebo group.

Median duration of treatment was 40.4 weeks in the everolimus group and 19.6 weeks in the placebo group.

Quality of life: No difference between groups and no worsening in FACT-G total scores

Health-related quality of life (HRQoL) was measured with Functional Assessment of Cancer Therapy–General (FACT-G). In the pre-specified analysis (≥ 7 points minimal important difference [MID]), no statistical differences were observed between the treatment arms in time to deterioration (TTD) of FACT-G total score (HR, 0.81; 95% CI, 0.55 to 1.21).

In the post-hoc analysis (≥ 3 point MID), TTD for the physical (HR, 1.01; 95% CI, 0.69 to 1.53), social (HR, 0.72; 95% CI, 0.45 to 1.28), emotional (HR, 0.57; 95% CI, 0.36 to 0.93) and functional (HR, 0.94; 95% CI, 0.60 to 1.46) well-being subscale scores were maintained for everolimus versus placebo. In the linear mixed model, FACT-G total score at week 8 was 79.5 (95% CI, 77.7 to 81.3) for everolimus and 80.0 (95% CI, 77.6 to 82.5) for placebo, declining to 75.7 (95% CI, 73.2 to 78.2) for everolimus and 77.8 (95% CI, 73.5 to 82.1) for placebo at week 48.

Safety: Moderate toxicities, consistent with those seen in other tumour types

Safety analysis was performed at the time of the first data cut-off, November 2014. On-treatment deaths, defined as those occurring during receipt of study medication or within 30 days of discontinuing therapy, were similar between the treatment groups: seven deaths (3.5%) occurred in the everolimus group and three (3.1%) occurred in the placebo group. Four of the seven deaths in the everolimus group were considered to be related to the primary disease and/or disease progression. Of the remaining three deaths, one was due to respiratory failure, one was due to septic shock, and one was due to cardiac failure.

The most common adverse events were stomatitis, diarrhea, fatigue, infections, rash, and peripheral edema. The most common grade 3 or 4 drug-related adverse events included stomatitis, diarrhea, infections, anemia, and fatigue.

In the everolimus group and placebo group, 59 (29%) and seven (7%) patients, respectively, discontinued study treatment due to adverse events. Treatment discontinuation attributed to grade 3 or 4 adverse events were reported in 36 (18%) and five (5%) patients in the everolimus and placebo group, respectively. The most frequent adverse events leading to treatment discontinuation in everolimus versus placebo were stomatitis (3% versus 0%), gamma-glutamyl transferase increased (1.5% versus 0%), and diarrhea (1.5% versus 0%). Non-infectious pneumonitis occurred in 32 patients (16%) in association with everolimus treatment. Grade 3 pneumonitis occurred in three patients (1%) and no grade 4 cases were reported.

On-treatment death was similar (3.5% versus 3.1%). The death rate due to toxicity with everolimus was 1.5%.

The Committee noted that moderate toxicities experienced with everolimus for NETs GIL were consistent with those seen in other tumour types.

Limitations: Some potential sources of bias

Although data were collected via data management systems, data were analyzed by the funder's (Novartis Pharmaceuticals Corporation) statistical team. This may lead to detection bias.

With an end point of progression (and not OS), inadvertent unblinding may occur because of the appearance of adverse events due to the drug. This may lead to detection bias.

As with many randomized controlled trials (RCTs), only the healthiest patients within a disease are eligible to be enrolled in a trial. This may lead to sampling bias. Due to the inclusion of only the best of the best (in this case, WHO performance score of 0 or 1), generalizability of the results of the trial to all those with the disease condition may not be possible.

The use of subsequent treatments following the treatments under study may impact the OS of patients under treatment. This can happen due to the type of subsequent treatment used in second line or due to sequencing of treatments.

Comparison with other literature and ongoing trial: Different patient populations in RADIANT-4 and PROMID studies preclude indirect comparison; ongoing trial compares everolimus, somatostatin analogues, and combination therapy

The Committee acknowledged the comparison with other literature and noted that the differences in the patient population in the RADIANT-4 (gastrointestinal and lung, only non-functional NETs) and PROMID (midgut, functional and non-functional NETs) studies precluded an indirect comparison of everolimus to octreotide LAR. pERC also noted one ongoing phase 2 trial, LUNA, which compares everolimus, SSAs, and combination therapy in adult patients with advanced (unresectable or metastatic) neuroendocrine carcinoma (typical and atypical) of lung and thymus.

Registered clinician input: None received

pERC noted that no registered clinician input was received for this review.

Need: Absence of reliably effective therapeutic alternatives

NETs are a heterogeneous group of cancers arising from a variety of anatomic sites with approximately 50% of GI and 25% of lung origin. The incidence of NETs has been steadily increasing over the past four decades, although the overall incidence of metastatic NETs appears to have remained stable. Data from the Ontario Cancer Registry demonstrated an increase in the incidence of NETs in Ontario from 2.48 to 5.86 per 100,000 per year from 1994 to 2009, with metastatic disease documented in 20.8% at presentation and developing subsequent to diagnosis in an additional 38%, although the overall incidence of metastatic NETs appears to have remained stable. Incidence was observed to increase significantly after the age of 50 years, peaking in those older than 70 years.
There is no current standard of care for the treatment of non-functional NETs GIL. Patients may be treated with BSC, SSA, or chemotherapy.

PATIENT-BASED VALUES

Values of patients with neuroendocrine tumours of gastrointestinal or lung origin: Shrink tumours, control symptoms, and different treatment options

From a patient's perspective, the physical and emotional impact of living with NETs GIL was varied. Respondents interviewed reported that living with their NETs cancer makes life uncertain because of the terminal nature of the disease and no cure being available. Respondents reported that the biggest challenge they face is dealing with disease symptoms such as fatigue and/or lack of stamina, diarrhea, bloating, and abdominal cramps. Additional challenges reported by respondents include being sick for a long time due to misdiagnosis and having to make changes in their life because of their cancer.

Respondents also stated that NETs cancer has a negative impact on patients' quality of life. All respondents interviewed indicated that their energy levels were affected negatively by their NETs cancer and, as a

result, they have less energy and more fatigue, which affects their ability to engage in leisure and social activities, travel, and work.

For respondents who have not used everolimus, the expectation is that the drug would shrink tumours and that not as much tissue would have to be removed through surgery. In addition, the treatment would provide better symptom control for bloating, diarrhea, constipation, and energy levels. The Committee noted that disease control and more treatment options were most important to patients. pERC agreed that everolimus offers another treatment option, with PFS benefits, and is a clinically well-known drug.

Patient values regarding treatment: Reduction in disease progression, tumour shrinkage, decrease in disease symptoms, improved wellness; receive clear and fulsome information from physician

For respondents who have experience with everolimus, the greatest benefit that respondents reported with taking everolimus was a reduction in the progression of their disease, followed by tumour shrinkage, a decrease in disease symptoms, and improved wellness. Two respondents also commented that they had stability in their disease. The most common side effects respondents found with taking everolimus were fatigue, followed by mouth sores and increased diarrhea. Respondents noted that they would like their doctors to explain all the side effects of the drug, not just the most common. They argued that having clear and fulsome information would allow patients to make fully informed treatment decisions.

ECONOMIC EVALUATION

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

The cost-effectiveness analysis and cost-utility analysis submitted to pCODR by Novartis Pharmaceuticals Canada Inc. compared everolimus plus BSC to BSC alone for patients with advanced (unresectable or metastatic), progressive non-functional GI or lung NETs.

Basis of the economic model: Partitioned survival model

The partitioned survival model comprised 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. The base-case analysis used a 10-year time horizon. Efficacy data were sourced from the RADIANT-4 trial. Utility values were based on a mapping study of data from the FACT-G quality-of-life questionnaire to the EuroQol Five-Dimensions (EQ-5D) using an algorithm developed in the United Kingdom (UK). Resource use was based on expert opinion. Cost information was sourced from UK and Canadian sources.

Drug costs: High drug costs

The list price for everolimus is $200.0850 per 10 mg tablet. At the recommended dose of 10 mg daily, everolimus costs $200.0850 per day, or $5,602.38 per 28-day course.

Cost-effectiveness estimates: Best estimate driven by revised clinical assumptions, primarily impacted by the overall survival assumptions in the post-trial period

The pCODR EGP's estimate of the incremental cost-effectiveness ratio is between $212,491 per quality-adjusted life-year (QALY) and $305,673/QALY; within this range, the best estimate would likely be $249,486/QALY.

The extra cost of everolimus is between $91,639 and $99,245. The incremental cost of everolimus is relatively stable; it is slightly impacted by the HR for OS and rate of hospitalization and ER visits. The factors that most influence the incremental cost include rates of hospitalization and ER visits, half-cycle correction not applied to cost of everolimus; pERC noted that incremental cost was slightly impacted by these factors. pERC also noted that the cost of everolimus was a driver to the incremental cost. The extra clinical effect of everolimus is between 0.305 QALYs and 0.701 QALYs (ΔE). The factors that most influence the incremental effectiveness include the HR for OS and the parametric distribution applied post-trial.

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, as the final overall survival analysis has not yet been reported. The EGP expressed concern regarding the magnitude of the benefit given the uncertainty around the
OS benefit. The EGP best estimate is driven by revised clinical assumptions, primarily affected by the OS assumptions in the post-trial period.

The main assumptions and limitations of the submitted model are reported below. The submitter did not consider SSAs as a comparator. Feedback from the pCODR Clinical Guidance Panel (CGP) suggested SSAs are an appropriate comparator, but SSAs such as octreotide and lanreotide were not considered by the submitter in its submitted economic analysis. A trial-based PFS Kaplan–Meier curve may have overestimated benefit. OS benefit prediction for everolimus compared with BSC is associated with uncertainty. The parametric distribution used to model OS did not accurately represent the trajectory of disease. 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 five years, the time horizon has little impact on the incremental cost-utility ratio. It was also noted that using a 15-year time horizon as opposed to a 10-year time horizon would have no impact on the incremental cost-effectiveness. The modelling of utility values does not accurately represent patients with NETs. 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 is 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. The EGP was unable to test the impact of time-dependent utility values. The resource use and associated costs were overestimated for BSC compared with everolimus. Feedback from the CGP suggested that several of the resource use assumptions may overestimate the costs associated with BSC.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Wastage, flat pricing, high cost per patient, and unknown duration of treatment

PAG noted that there is an unmet need for patients whose disease has progressed or relapsed and that everolimus will provide a treatment option for these patients, and it is already funded for patients with pancreatic NETs.

PAG had concerns with wastage when dose adjustments are made and a different tablet strength is required prior to the patient completing the strength initially provided.

PAG noted that there would be a small incremental budget impact due to the small number of patients, but treatment cost per patient is high and duration of treatment is unknown. The factors that most influence the budget impact analysis include the additional cost of drug for everolimus, the prevalence of GI and/or lung NETs in Canada, assumptions regarding market share, and constant uptake of the drug.

PAG stated that the flat pricing structure (for 2.5 mg, 5 mg, and 10 mg tablets) is a barrier to implementation.

DRUG AND CONDITION INFORMATION

Drug Information	• Everolimus is an orally administered inhibitor of the mammalian target of rapamycin (mTOR) • 10 mg tablet reviewed by pCODR • Recommended dosage of 10 mg tablet once daily (oral)
Cancer Treated	• Neuroendocrine tumours (NETs) of gastrointestinal or lung origin (GIL)
Burden of Illness	• The incidence of NETs has been steadily increasing over the past four decades, although the overall incidence of metastatic NETs appears to have remained stable • Data from the Ontario Cancer Registry demonstrated an increase in the incidence of NETs in Ontario from 2.48 to 5.86 per 100,000 per year from 1994 to 2009, with metastatic disease documented in 20.8% at presentation and developing subsequent to diagnosis in an additional 38%
Current Standard Treatment	• Best supportive care • Somatostatin analogues
Limitations of Current Therapy	• Absence of reliably effective therapeutic alternatives • Cytotoxic chemotherapy is rarely considered due to conflicting evidence documenting effectiveness and potential unfavourable impacts on quality of life

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. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy Thompson, Pharmacist
Valerie McDonald, Patient Member Alternate
Carole McMahon, Patient Member
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Danica Wasney, Pharmacist

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

- Valerie McDonald, who did not vote due to her role as a patient member alternate.

Avoidance of conflicts of interest

All members of pERC 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 everolimus for neuroendocrine tumours of gastrointestinal or lung origin, through their declarations, six members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was 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, registered clinician, 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 pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

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.

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