pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The 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-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

Providing Feedback on this Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *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)

Funding Request:
Patients with well- or moderately differentiated neuroendocrine tumours of pancreatic origin (pNETs) in patients with unresectable, locally advanced or metastatic disease.

Submitted By:
Novartis Pharmaceuticals Canada Inc.

Manufactured By:
Novartis Pharmaceuticals Canada Inc.

NOC Date:
February 2, 2012

Submission Date:
February 27, 2012

Initial Recommendation Issued:
July 6, 2012

RECOMMENDATION	The pCODR Expert Review Committee (pERC) recommends funding everolimus (Afinitor) conditional on the cost-effectiveness of everolimus being improved to an acceptable level. Funding should be for the treatment of patients with progressive, unresectable, well- or moderately differentiated, locally advanced or metastatic pancreatic neuorendocrine tumours, with WHO performance status of 0 or 1. Treatment should be continued until disease progression. The Committee made this recommendation because it was satisfied that there is an overall clinical benefit of everolimus based on the magnitude of the observed progression-free survival difference between everolimus and placebo. However, the Committee noted that everolimus could not be considered cost-effective at the submitted price and the Economic Guidance Panel's estimates of the range of incremental cost-effectiveness ratio.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given pERC was satisfied that there is a net clinical benefit of everolimus, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of everolimus to an acceptable level. **Sequential Use of mTOR Inhibitors and Tyrosine Kinase Inhibitors** There is no evidence available on the clinical benefit or cost effectiveness of sequential treatment with mTOR inhibitors and tyrosine kinase inhibitors in the treatment of pancreatic neuroendocrine tumours. Therefore, pERC is unable to make an informed recommendation on funding everolimus for patients after progression on sunitinib. However, pERC considered that it would be reasonable to use an mTOR inhibitor such as everolimus in patients intolerant of first-line treatment with a tyrosine kinase inhibitor, such as sunitinib (or vice versa).

SUMMARY OF pERC DELIBERATIONS

pERC noted that, historically, there has been no standard treatment for pancreatic neuroendocrine tumours (pNETs) and that effective therapeutic options for patients with pNETs are limited. pERC considered that given the lack of randomized controlled trial evidence supporting systemic therapies for pNETs, at the time, a placebo comparator could be considered appropriate. However, pERC also recognized that sunitinib, which was recently approved by Health Canada for pNETs, is also a relevant comparator in this setting.

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

pERC discussed the results of the randomized controlled trial included in the pCODR systematic review, which compared everolimus with placebo (RADIANT-3, Yao 2010). pERC considered that RADIANT-3 was an appropriately conducted trial that followed its pre-specified analysis plan, giving pERC confidence in the trial results. The Committee considered that the hazard ratio and the magnitude of the absolute difference in progression-free survival for everolimus compared with placebo were both statistically significant and clinically meaningful. pERC also noted that a consistent benefit in progression-free survival was observed across pre-specified subgroups. There was no statistically significant difference in overall survival. However, pERC noted that results were likely confounded by the cross-over of some patients from the placebo group to everolimus following disease progression, although further collection of survival data is ongoing.

pERC also considered the safety of everolimus based on grade three/four adverse events and the most frequently observed adverse events in RADIANT-3. pERC considered that the toxicity profile, which included fatigue, stomatitis and diarrhea, was consistent with the use of everolimus in other indications and that the majority of adverse events are manageable through dose reductions. However, pERC noted that dose reductions would not result in an accompanying decrease in drug costs because the prices of 2.5 mg, 5 mg and 10 mg tablets are the same and tablets are not scored to allow for splitting.

pERC emphasized that one of the main limitations of RADIANT-3 was the lack of information on quality of life and that it would be important to understand if quality of life is maintained for patients receiving everolimus given that overall survival data are likely confounded. Also, patients receiving everolimus had more toxicities compared with patients receiving placebo and it is unclear if quality of life is not diminished by these toxicities. Collection of quality of life data in clinical trials for advanced disease is particularly important when quality of life is an important factor in treatment selection and response assessment. However, in the absence of quality of life data, pERC reviewed patient advocacy group input, which included direct experiences of five patients who had received everolimus for pNETs. These patients perceived that there was a benefit to everolimus and, with the exception of one patient, were able to tolerate side effects associated with everolimus. While pERC appreciated having the direct experiences of patients to review, the small number of patient experiences was noted and pERC suggested that other approaches to identifying patients who may be able to provide useful input, such as global patient group collaborations, may be appropriate in a condition such as pNETs where there are only a small number of patients in Canada at the time of evaluation by pERC.

Overall, pERC considered that everolimus aligned with patient values. Patient advocacy group input on everolimus indicated that patients with pNETs value the outcome of progression-free survival as a measure of disease stability, which was demonstrated to be clinically and significantly improved in the RADIANT-3 trial. Patients also indicated they are willing to tolerate significant side effects if everolimus is able to control pNETs.

pCODR's Provincial Advisory Group considered sunitinib to be a relevant comparator given its recent availability to treat pNETs in Canada. pERC noted that there are no head-to-head trials comparing everolimus with sunitinib and that cross-trial comparisons are challenging. However, pERC considered that the toxicity profiles of sunitinib, a tyrosine kinase inhibitor, and everolimus, an mTOR inhibitor,

differ and that they each has a unique mechanism of action. As such pERC considered that it would be important for clinicians and patients to be able to choose either drug as a first-line treatment option.

pERC also discussed the fact that sequential use of everolimus and sunitinib could have a significant impact on drug costs. In the absence of clinical and cost-effectiveness evidence in this situation, pERC could not make a recommendation on the sequential use of everolimus following disease progression on sunitinib. However, pERC considered that it would be reasonable to use an mTOR inhibitor following intolerance of a tyrosine kinase inhibitor or vice versa (i.e., tyrosine kinase inhibitor after an mTOR inhibitor.

pERC discussed the cost-effectiveness of everolimus and noted that the manufacturer's estimates were substantially lower than the pCODR Economic Guidance Panel's estimates. The Economic Guidance Panel considered that the structure of the economic model was inadequate, primarily because the manufacturer's model assumed that there was a similar risk of dying before and after disease progression. The pCODR Gastrointestinal Clinical Guidance Panel considered this assumption unrealistic from a clinical perspective and pERC agreed. pERC accepted the Economic Guidance Panel's conclusions and estimates of cost-effectiveness, which are likely even higher than estimated, recognizing that their estimates were limited by the structure of the economic model that was provided. Therefore, pERC concluded that everolimus was not cost-effective at the submitted price and the Economic Guidance Panel's estimates.

When considering the feasibility of implementing a recommendation for everolimus, pERC noted that there are a small number of patients with pNETs, which may lead to it being affordable from a jurisdictional perspective. pERC further discussed that once prevalent patients with pNETs are treated with newer therapeutic options such as everolimus, there will likely be only a small number of new incident cases going forward annually.

EVIDENCE IN BRIEF

pERC deliberated upon a pCODR systematic review, other literature in the Clinical Guidance Report providing 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 Tumor Society Canada, CNETS) and input from pCODR's Provincial Advisory Group.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the effect of everolimus on patient outcomes including overall survival, progression-free survival, quality of life, and harms compared to standard treatment or placebo in patients with unresectable locally advanced or metastatic well- or moderately differentiated progressive pancreatic tumour.

Studies included

The pCODR systematic review included one double-blind randomized controlled trial (RADIANT-3, Yao 2010) comparing everolimus with placebo in 410 patients with unresectable locally advanced or metastatic well- or moderately differentiated pancreatic neuroendocrine tumours that had progressed within the last 12 months. pERC noted RADIANT-3 was an appropriately conducted trial. pERC noted that it followed its pre-specified statistical analysis plan and did not include unplanned multiple looks at the data, giving the Committee confidence in the observed trial results.

Patient populations: Moderately-differentiated tumours and WHO performance status 0 or 1

RADIANT-3 included patients with unresectable locally advanced or metastatic well- or moderately differentiated pancreatic neuroendocrine tumours that had progressed within the last 12 months. pERC noted that the majority of included patients, approximately 83%, had well-differentiated tumours.

Patients with WHO performance status scores of 0, 1 or 2 were eligible to be included in RADIANT-3, however, only about 3% of included patients had a WHO performance status score of 2; of the remaining patients two-thirds had a WHO performance status score of 0 and one third had a score of 1. pERC therefore considered that the RADIANT-3 evidence primarily supported the use of everolimus in patients with WHO performance status scores of 0 or 1.

Key efficacy results: Clinically meaningful improvement in progression-free survival

Efficacy outcomes deliberated upon by pERC included overall survival, the risk of death and progression-free survival. Progression-free survival was the primary endpoint of RADIANT-3 and everolimus was associated with a statistically significant increase in progression-free survival compared with placebo [11 months versus 4.6 months; hazard ratio = 0.35, 95% CI: 0.27 to 0.45]. pERC considered the magnitude of this difference to be clinically meaningful. In addition, everolimus was associated with a consistent improvement of the progression-free survival across subgroups. pERC discussed that differences in overall survival were not statistically significant either in the main analysis or in an analysis adjusted for cross-over. However, pERC considered that collection of survival data was ongoing and the analysis is likely confounded by the cross-over of patients in the placebo group to open-label everolimus, following disease progression.

Quality of life: No information available in RADIANT-3

pERC noted that the RADIANT-3 study did not evaluate the effect of everolimus on quality of life. pERC considered this to be a significant short-coming of the study given its importance to patients. Furthermore, pERC discussed that in the absence of a clear overall survival benefit, it would be important to understand if changes in quality of life are observed in patients receiving everolimus. However, pERC concluded that the magnitude of the observed difference in progression-free survival between everolimus and placebo was such that the Committee had confidence in the net overall clinical benefit of everolimus.

Safety: Side effects tolerated or manageable through dose reductions

In RADIANT-3, grade three and grade four adverse events that occurred more frequently in the everolimus group compared with the placebo group were anemia, hyperglycemia, diarrhea and stomatitis. Other common adverse events that were higher in the everolimus group than the placebo group included rash, fatigue, peripheral edema and nausea. pERC discussed these adverse events and noted that they appeared consistent with those observed for other indications where everolimus is used and that many would be manageable in clinical practice through dose reductions. Furthermore, pERC noted that patient advocacy group input indicated patients were generally willing and able to tolerate the side effects associated with everolimus.

Comparator information: Side effects may differ from sunitinib but no direct comparison

pERC discussed that although RADIANT-3 compared everolimus with placebo, sunitinib is also a relevant comparator and that pCODR's Provincial Advisory Group was interested in any differences between everolimus and sunitinib. pERC noted that everolimus, an mTOR inhibitor, and sunitinib, a tyrosine kinase inhibitor, each has a unique mechanism of action. pERC discussed that there are no randomized controlled trials directly comparing everolimus with sunitinib in patients with pNETs and that there are limitations in making cross-trial comparisons. pERC noted that a published abstract describing an indirect comparison of everolimus and sunitinib in patients with pNETs indicated no significant differences between the two therapies in progression-free survival. While the indirect comparison did not evaluate safety, based on cross-trial comparisons and different mechanisms of action, pERC determined that the toxicity profile of everolimus may differ from that of tyrosine kinase inhibitors such as sunitinib. Therefore, pERC considered that it would be important that clinicians and patients be able to choose one or the other as a first-line treatment option for individual patients.

Need: Treatment option with different mechanism of action and side effect profile

pERC noted that, historically, there has been no standard treatment for pancreatic neuroendocrine tumours (pNETs) and that effective therapeutic options for patients with pNETs are limited. pERC considered that given the lack of randomized controlled trial evidence supporting systemic therapies for pNETs, at the time, a placebo comparator was considered appropriate. However, pERC also recognized that it was important to consider everolimus in light of recently available and relevant treatments for pNETs, such as sunitinib. pERC noted that, in addition to providing a treatment option that has demonstrated a clinically meaningful improvement in progression-free survival in an appropriately conducted randomized controlled trial, everolimus has a different mechanism of action and appears to

have a different side effect profile compared with sunitinib, based on cross-trial comparisons that should be interpreted with caution.

PATIENT-BASED VALUES

Values of patients with pNETs: Disease stabilization and improved quality of life
pERC considered patient advocacy group input indicating that patients with pNETs valued the outcome of progression-free survival and having stable disease. As well, patients would be willing to tolerate significant side effects if a treatment were able to control pNETs. pERC noted that progression-free survival was demonstrated to be statistically significantly improved in the RADIANT-3 trial and pERC also considered the magnitude of difference to be clinically significant. Patient input also indicated that treatments improving quality of life would provide an additional benefit that is valued by patients. pERC also noted that patients with pNETs experience other challenges such as delays in diagnosis or misdiagnosis of pNETS and may be unable to continue working due to symptoms related to pNETs.

Patient values on treatment: Tolerable side effects based on direct patient experience
pERC discussed that patients were willing to tolerate adverse events associated with an effective treatment and reviewed the toxicity profile of everolimus. pERC noted that many adverse events could be managed through dose reductions. In addition, pERC reviewed information provided through patient advocacy group input on the direct experiences of five patients who had received everolimus for pNETs. These patients perceived that there was a benefit to everolimus and, with the exception of one patient, were able to tolerate side effects associated with everolimus. While pERC appreciated having the direct experiences of patients to review, it was noted that this was a very small number of patient experiences and that other approaches to identifying patients, such as global collaborations, may be appropriate in a condition such as pNETs where there are only be a small number of patients in Canada at the time of evaluation by pERC.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility
The pCODR Economic Guidance Panel assessed an economic model that estimated the cost-effectiveness and cost-utility of everolimus plus best supportive care compared to placebo plus best supportive care for patients with progressive, unresectable locally advanced or metastatic, well- and moderately-differentiated pancreatic neuroendocrine tumors. pERC considered this was an appropriate comparison but also noted that sunitinib was also a relevant comparator and no comparison with sunitinib was provided by the manufacturer.

Basis of the economic model: clinical and economic inputs
Costs included drug costs and healthcare costs associated with routine follow-up for patients receiving active treatment, disease progression, routine health care resources involved in best supportive care and death. Costs associated with management of serious adverse events were also considered.

Key clinical effects included progression-free survival and overall survival estimates from RADIANT-3, a randomized controlled trial comparing everolimus with placebo. The biggest influence on both QALYs and life years was the extrapolated estimate of survival following tumour progression.

Drug costs: Dose reductions do not lead to lower drug costs
Everolimus costs $186.00 per 2.5 mg, 5 mg, or 10 mg tablets, at the list price. At the recommended dose of 10 mg per day, the average cost per day in a 28-day course of everolimus is $186.00 and the average cost per 28-day course is $5,208. pERC noted that the price of everolimus tablets is the same regardless of dose and tablets are not scored to allow for splitting and, therefore, dose reductions would not result in a corresponding decrease in drug costs. In addition, dose reductions due to toxicities may also result in wastage because tablets are not scored to allow for splitting and a new prescription would be required.

Sunitinib is available as 12.5 mg, 25 mg, and 50 mg capsules at a cost of $63.15, $126.30, and $252.61 respectively. At the recommended dose of 37.5 mg per day, the average cost per day in a 28-day course of sunitinib is $189.45 and the average cost per 28-day course is $5,305.

Cost-effectiveness estimates: Inadequate model structure and invalid clinical assumptions made by manufacturer

The Economic Guidance Panel's estimate of the incremental cost-effectiveness ratio is between $165,129 per QALY and $273,781 per QALY when everolimus plus best supportive care is compared to placebo plus best supportive care. However, pERC noted that the Economic Guidance Panel's estimates were unable to fully account for structural limitations identified in the submitted model and therefore, thus these estimates may still underestimate the actual incremental cost-effectiveness ratio. pERC also noted that the Economic Guidance Panel had requested data from the manufacturer to address limitations in the model but the Panel was not able to use the data that were provided to produce a better estimate. While the Economic Guidance Panel's estimates were considerably higher than the manufacturer's estimates of cost-effectiveness, pERC accepted the Panel's estimates and agreed with the Panel that the submitted model structure was inadequate, based on invalid clinical assumptions. As a result, pERC concluded that everolimus could not be considered cost-effective at the submitted price and the Economic Guidance Panel's estimates of the range of incremental cost-effectiveness ratios.

pERC discussed that a major limitation of the manufacturer's estimates was that the manufacturer had assumed that a patient's risk of dying before tumour progression and the patient's risk of dying after tumour progression were similar, implying that patients continued to benefit from the drug even after tumour progression occurred and the drug has been stopped. pERC agreed that this was not an appropriate assumption and further noted that the pCODR Gastrointestinal Clinical Guidance Panel did not consider the manufacturer's assumption to be clinically realistic. pERC also noted that a large proportion (>76%) of the gain in life expectancy was based on extrapolated data and not actual data, biasing results in favour of everolimus by overestimating the clinical effect of everolimus. The Economic Guidance Panel re-analyses shortened the time horizon to better align with clinical data.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Dose reductions, prevalence estimates and sequential use

pERC considered potential factors influencing the budget impact and noted that while dose reductions may occur with everolimus in practice, this would not lead to a corresponding reduction in drug costs because the cost of a 2.5 mg, 5 mg and 10 mg tablet is the same. pERC also considered that the annual number of patients with pNETs who would need to be treated with everolimus would potentially be low once prevalent cases were treated as there are only be a small number of incident cases diagnosed each year. pERC also noted that use in the adjuvant setting could increase budget impact; however, there are no randomized controlled trials evaluating everolimus as an adjuvant treatment.

pERC also discussed that sequential use of everolimus and sunitinib could potentially have a large budget impact. However, pERC noted that there are no randomized controlled trials evaluating sequential use of sunitinib and everolimus in pNETs and in the absence of clinical and cost-effectiveness data, pERC could not make an informed funding recommendation based on sequential use of funding everolimus for patients after progression on sunitinib. However, pERC considered that it would be reasonable to use a mTOR inhibitor following intolerance of a tyrosine kinase inhibitor or vice versa.

DRUG AND CONDITION INFORMATION

Drug Information	• Inhibitor of mammalian target of rapamycin (mTOR) • 2.5 mg, 5 mg and 10 mg tablets reviewed by pCODR • Recommended dosage of 10 mg administered orally once daily
Cancer Treated	• Advanced or metastatic well- and moderately-differentiated pancreatic neuroendocrine tumours.
Burden of Illness	• 1% to 4% of pancreatic neoplasms. Incidence approximately 0.2 per 100,000 but also appears to be increasing. The majority of patients (> 80%) present with metastatic or locally advanced disease.
Current Standard Treatment	• No standard treatment. Treatment approach is multi-disciplinary and options may include surgery, Peptide Receptor Radionucleotide Therapy and systemic chemotherapy. Sunitinib recently received regulatory approval in the treatment of pNETs.
Limitations of Current Therapy	• Surgery is only curative for patients presenting with early stage disease • Peptide Receptor Radionucleotide Therapy is not easily accessible to patients • Systemic chemotherapy has associated toxicities and rigorous clinical trials supporting a benefit have not been conducted • Sunitinib, has recently become available but some patients experience side effects associated with tyrosine kinase inhibitors, e.g. hand-foot syndrome

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee 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. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Lister, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Jo Nanson, Dr. Tallal Younis and Dr. Peter Venner who were not present for the meeting

Avoidance of conflicts of interest

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

Information sources used

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

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Novartis, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information has been redacted in this recommendation, if applicable, and publicly available guidance reports.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers 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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