PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Everolimus (Afinitor) for pancreatic neuroendocrine tumours (pNETs)

August 30, 2012

3. Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Everolimus (Afinitor) for pancreatic neuroendocrine tumours
Role in Review:	Submitter and Manufacturer
Organization Providing Feedback:	Novartis Pharmaceuticals Canada Inc.

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees __X_ agrees in part ____ disagree

Novartis, the Manufacturer, agrees in part with the following initial recommendation related to the following statements made in this document:

SUMMARY OF pERC DELIBERATIONS & ECONOMIC EVALUATION & EVIDENCE IN BRIEF (Overall Clinical Benefit): *"… historically, there has been no standard of care…"& "However, pERC also recognized that sunitinib, which was recently approved by Health Canada for pNETs, is also a relevant comparator in this setting…"*

Both pNET trials were conducted between 2007 and 2009 and there were no other therapeutic options for this population setting. There are few Canadian treatment guidelines or protocols for the medical management of advanced NET, and none specific for pancreatic NET. The National Comprehensive Cancer Network (NCCN) recommendations for management of locoregional unresectable disease and/or distant metastases with symptoms, clinically significant tumour burden or progressive disease are symptom management and treatment with everolimus (10 mg/day), sunitinib (37.5 mg/day), cytotoxic chemotherapy, hepatic regional therapy, cytoreductive surgery or octreotide (if not already receiving)[iii]. In addition, as per CADTH HTA guidelines, comparators should be considered "usual care" or "recommended care."[iv] As such, it is unclear why sunitinib is considered to be a relevant comparator.

EVIDENCE IN BRIEF (Economic Evaluation): *"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." & "… a new prescription would be required…"*

Most oral cytotoxic agents cannot be split and as such new claims are dispensed at an additional cost. Hence, these comments can be made for most oral cytotoxic agents. As per RADIANT-3, AE management was also managed by dose interruption, which may offset any additional costs for patients requiring a "dose-reduced" claim.

EVIDENCE IN BRIEF (Economic Evaluation): *"Drug costs: Dose reductions do not lead to lower drug costs"*

The maximum, approved everolimus dose for patients with pNET is 10mg daily[i] and duration of treatment was reported from the RADIANT-3 trial, thus allowing funding jurisdictions to determine the maximum budgetary impact of funding everolimus in pNET with certainty.

EVIDENCE IN BRIEF (Economic Evaluation): "….*a major limitation of the manufacturer's estimates was that the manufacturer assumed that a patient's risk of dying before tumor progression and dying after tumor progression is the same…"*

The Manufacturer model does not assume that the patient's risk before and after tumour progression is the same. The analysis presented was derived from two statistical analyses; one deriving the PFS and the second deriving the overall survival determined through the RPSFT analysis. Since the model is

populated on a partitioned survival analysis, it cannot be assumed that the probabilities are the same prior to and post progression and should inherently account for different mortality rates prior and post progression. In the clinical trial, the definition of a PFS event overlaps with the definition of an OS event, i.e. PFS included either progressed or dead, whichever was achieved first. The model accounts for this definition and as such portions out patients in either the stable or death state. As patients in progression state could only transition to the death state, the risk of death is inherently different for patients transitioning from progression state compared to patients transitioning from the stable state.

EVIDENCE IN BRIEF (Economic Evaluation): "…re-analyses shortened the time horizon to better align with clinical data…"
We acknowledge the uncertainty that can be raised in extrapolation. Following CADTH HTA guidelines, extrapolation until death is recommended in order to capture all costs and benefits associated (CADTH HTA guidelines, 2006). In addition, the current appraisal appears to be inconsistent with previous assessment in pNET, whereby extrapolation and re-adjustment to align with clinical data was not termed as a major concern. In regards to clinical data availability, adjustment to a 3-year time horizon is limiting, as correctly highlighted in the clinical guidance report, in that the final OS analysis in the RADIANT 3 will be conducted once 250 events would be reached. While the analysis will unlikely demonstrate OS benefit due to the high cross-over (73% of placebo patients moved to the everolimus arm), it certainly suggests that patients can live beyond the current re-adjusted time horizon.

We urge the pERC to reconsider the above points, mainly the assumption regarding the risk of death prior and post progression whereby the ICER estimates derived is not underestimated as well as the shorter time horizon which is inconsistent with previous appraisals and does not reflect the latest reported overall survival of patients treated with everolimus in the RATIANT 3 study.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____ Support conversion to final recommendation.

Recommendation does not require reconsideration by pERC.

__X__ Do not support conversion to final recommendation.

Recommendation should be reconsidered by pERC

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
1 and 3	RECOMMENDATION & EVIDENCE IN BRIEF (Overall Clinical Benefit)	P1, 1, Line 6 & P3, 8, Line 1	*"…neuroendocrine tumours, with WHO performance status of 0 or 1."* **Suggested edit:** *"…neuroendocrine tumours, with WHO performance status of* 0, 1 or 2.
As per the product monograph[i] and the pivotal clinical trial publication, patients included in the RADIANT 3 study[ii] had WHO performance status of 0, 1 or 2. As such this statement inadequately addresses the population eligible for treatment with everolimus. This patient population was considered under the Clinical Guidance report, section 3.3, Evidence-Based Considerations for a Funding Population. There is no evidence to exclude patients with WHO performance status of 2 in the final recommendation.			
1/6	POTENTIAL NEXT STEPS FOR STAKEHOLDERS, SUMMARY OF pERC DELIBERATIONS & ADOPTION FEASIBILITY	P1, 1, Line 12 P3, 2, line 4 P6, 2, Line 5	*"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)."* **Suggested edit:** "However pERC considered that it would be reasonable to use either everolimus or sunitinib when a patient is intolerant to the other as first line treatment"
The sentence, as written, introduces a bias for use of everolimus after sunitinib, which is inconsistent with the overall pCODR recommendation, the patient population in the RADIANT 3 trial, and the Health Canada approved indication. There is no clinical data on sequential treatment use between those two agents. It should also be noted that in the RADIANT 3 trial, the patient population differed from patients in the A6181111 trial. More than 50% of patients (221/410) in RADIANT 3[ii] were treatment-naïve. Subgroup analysis demonstrated an equal benefit between patient pretreated with chemotherapy or not.			
2	SUMMARY OF pERC DELIBERATIONS	2, Line 10	*"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."* **Suggested edit:** "However, pERC noted that results were likely confounded by the cross-over of the majority of patients (73%) from the placebo group to everolimus following disease progression, although further collection of survival data is ongoing."

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
It is important to point out that the majority of patients rather than "*some patients*" from the placebo group crossed over to the everolimus arm, i.e. 73% of patients crossed over.			
2	SUMMARY OF pERC DELIBERATIONS	5, Line 3	*"…which demonstrated to be clinically and significantly improved in the RADIANT-3 trial."* **Suggested edit:** "…which demonstrated to be clinically and statistically significant improved in the RADIANT-3 trial."
As per Afinitor pNET indication: …statistically significant improvement in PFS in patients with pNET.			
6	ADOPTION FEASIBILITY	4, Line 6	*"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."*
As per the indication, everolimus cannot be used in this setting. There are NO registration trials currently ongoing to assess the efficacy of everolimus in this setting; as such this statement is misleading.			

References

[i] Afinitor product monograph: May 15 2012

[ii] Yao et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011: 364(6):514-23

[iii] National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors. Version 1.2011.

[iv] CADTH HTA guidelines, 2006

[v] Sutent product monograph: February 8, 2012

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

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

Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

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

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the

Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

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

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

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

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

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.