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 Neuroendocrine Tumours of Gastrointestinal or Lung Origin

December 1, 2016

Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	AFINITOR® (everolimus) for GI/LUNG NETs
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	Novartis Pharmaceuticals

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

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

Please explain why the* Submitter (or the Manufacturer of the drug under review, if not the Submitter) *agrees, agrees in part or disagrees with the initial recommendation.

Novartis Pharmaceuticals generally agrees with the initial recommendation for Afinitor GI/LUNG NET. The pCODR Expert Review Committee (pERC) recognizes the unmet medical needs in this patient population and that systemic therapy with AFINITOR® is aligned with patients' values. In addition, the recommendation also recognizes the importance of additional treatment options for patients with neuroendocrine tumours of GI and Lung origins. Afinitor® (everolimus) has shown impressive, clinically and statistically meaningful results in the RADIANT-4 trial, all the while maintaining quality of life in patients with non-functional GI/LUNG NETs.

Novartis however disagrees with the ICER reassessment in the Economic Guidance Report. The Economic Guidance Panel used 2 arbitrary figures for the hazard ratio (HR) of Overall Survival (OS) (0.80 and 1.0) in its reassessment. In the EGP re-analysis, using 0.8 as the base case estimate results in an inflated ICER. Although the OS data from RADIANT-4 was still immature at the time of the 2 interim OS analyses, the pERC recognized a trend in the OS data. Therefore, Novartis' opinion that the ICER assessment provided as part of its submission to pCODR using HR estimates from the RADIANT-4 trial is more appropriate. The EGP should have performed re-analyses and provide the ICER based on hazard ratios reported in the first and second data cut-offs of the RADIANT-4 trial (i.e. 0.64 and 0.73) to determine the threshold.

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.

X	Support conversion to final recommendation. Recommendation does not require reconsideration by pERC.	____	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
Economic Guidance Report, pg 5,	Section 1.4 Detailed highlights of the EGP analysis;	Bullet point #2	The hazard ratio in the November 2015 data cut off was 0.73. pCODR HR value of 0.80 seems to be an arbitrary estimate resulting in an inflated ICER in the EGP Re-analysis Although the OS data from RADIANT-4 was still immature at the time of the 2 interim OS analyses, the pERC recognized a trend in the OS data. Therefore, Novartis is of the opinion that the ICER assessment provided as part of its submission to pCODR using HR estimates from the RADIANT-4 trial is more appropriate. The EGP should have performed the re-analyse of the ICER based on the accurate HR of 0.73 as per November 2015 cut-off.
Initial recommendation, pg. 4; pg.9;	Adoption Feasibility / comments from Provincial Advisory Board	Pg. 4: 2nd paragraph; line #11 Pg. 9: Last paragraph	The PAG discussed the flat pricing structure for 2.5mg, 5mg and 10mg. Although Novartis recognized this barrier to implementation, Novartis would also like to reiterate that 4 different everolimus strengths (including the 7.5 mg strength) are included part of this submission. The 7.5 mg strength does not have the same price as the other strengths in most provinces.
Initial recommendation pg. 7	Limitations: Some potential sources of biais	Pg.7; 1st and 2nd paragraph	Novartis does not agree with the limitations raised by the pERC regarding the detection biais. The Novartis statistical team remained blinded as per very specific Standard

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
			Operating Procedures. In addition, primary endpoint of PFS was assessed by real time blinded independent central radiological assessment. Therefore, unblinding is unlikely and this reduces the likelihood of detection biais.

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Please note that new evidence will be 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 providing is eligible for a Resubmission, please contact the pCODR Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

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.cadth.ca/pcodr 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.cadth.ca/pcodr 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.cadth.ca/pcodr 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.