CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

(Registered Clinician)

Lenvatinib (Lenvima) for Renal Cell Carcinoma

January 4, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Lenvatinib in combination with everolimus for Advanced Renal Cell Carcinoma (RCC)
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Group, Clinical Group):	Clinical Group
Organization Providing Feedback	Dr. Christina Canil, Dr. Naveen Basappa and mRCC treating physicians affiliated with the Kidney Cancer Research Network of Canada.

**The pCODR program 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 eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☐ agrees ☐ agrees in part ☒ disagree

We do not believe that the expert opinion provided in the clinician submission by Dr.Canil et al, was duly considered in the recommendation provided by the Committee. Importantly, the KCRNC believes Lenvatinib in combination with everolimus addresses an unmet need for more active therapies with manageable adverse events that target escape resistance mechanisms to antiangiogenic therapy.

b) Please provide editorial feedback on the Initial Recommendation to aid in clarity. 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 #	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
P.1	pERC Recommendation	Paragraph 2	We do not believe that the expert opinion provided in the clinician submission by Dr.Canil et al, was duly considered in the recommendation provided by the Committee. All physicians who contributed to the submission actively participate in the Kidney Cancer Research Network of Canada (KCRNC) which promotes and facilitates kidney cancer research across Canada, enhancing the knowledge of kidney cancer and its treatment. A core part of our work is assessing and developing evidence for treatment consensus. Through our network, we have the necessary data and clinical experience required for the assessment and determination of clinical value of new treatments for mRCC. The pERC recommendation conflicts with our assessment of the value of this novel therapy. The KCRNC believes lenvatinib/everolimus is an effective treatment option for patients who require treatment for mRCC. We remain of the opinion that with the demonstrated efficacy of lenvatinib/everolimus, along with a safety profile that is both familiar and manageable, on balance the potential benefits of this combination therapy are substantial (outweighing the risks) and would have meaningful impact for our mRCC patients in this setting.
			<u>Place in Therapy:</u> The KCRNC is aligned to the clinical guidance panel review in terms of place in therapy of Lenvatinib: "Hope 205 permitted 1 prior TKI therapy as well as prior immunotherapy although only a small

			proportion of patients actually received both, a prior TKI and checkpoint inhibitor immunotherapy (2% and 4% in the lenvatinib/everolimus and everolimus arm, respectively). However, given the available data of other targeted agents and the completely different mechanism of action of lenvatinib/everolimus there is no reason why patients pretreated with 1 prior TKI and immunotherapy should not respond to lenvatinib/everolimus." We agree, and believe that lenvatinib/everolimus should be approved for second or third line therapy after 1 prior TKI or after TKI and immunotherapy.

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder would support this Initial Recommendation proceeding to Final pERC Recommendation ("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

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p.2	Summary of pERC Recommendations	Paragraph 1	Unmet Need: pERC concluded that "Given the availability of other treatments following progression on a VEGF-targeted therapy, pERC was uncertain whether Lenvatinib in combination with everolimus addresses an unmet need". We do not believe that the Committee has properly considered this key area in the proper context. While existing approved therapies have led to improved patient outcomes overall, durable responses are still infrequent and there remains an unmet need for more active therapies with manageable adverse events that target escape resistance mechanisms to antiangiogenic therapy. Evidence demonstrates that lenvatinib in combination with everolimus is a novel therapy that can meet that need in a way other approved therapies have yet to demonstrate.
p.4	Summary of pERC Recommendations	Paragraph 4	pERC concluded that "*… the magnitude of the benefit is uncertain compared with everolimus monotherapy or other currently available treatment option.*"

			The overall magnitude of superiority in overall response rate (ORR), and progression free survival (PFS) demonstrated in the HOPE-205 trial clearly favors the combination of lenvatinib+everolimus over everolimus alone. While we recognize that the HOPE-205 trial was not powered to detect a statistically significant overall survival (OS) benefit, we believe that the OS results observed in the trial (10 months for everolimus in combination with lenvatinib compared with everolimus alone) signal strongly that this therapy has much potential for patients in the 2nd line.
P.2	Summary of pERC Recommendations	Paragraph 1	We also note that the initial pERC recommendation is discordant with the recommendations made by pCODR's own Clinical Guidance Panel report where (Section 1.3): "The Clinical Guidance Panel concluded that there is a net overall clinical benefit to lenvatinib/everolimus compared with everolimus monotherapy for the second-line (after 1 prior VEGF-targeted therapy) treatment of advanced and metastatic RCC based on one randomized controlled phase Ib/II trial (HOPE-205) that demonstrated a clinically meaningful and statistically significant benefit in response rate, PFS and OS for lenvatinib/everolimus compared with everolimus."
p.3	Summary of pERC Recommendations	Paragraph 2	*"pERC noted that it is feasible to conduct a Phase III RCT in this setting".* Recognizing that there are very few head-to-head comparisons between currently approved drugs in the 2nd line, and given the relatively small patient population requiring 2nd line and 3rd line treatment, phase 3 trials in these settings might not be feasible. Also, Health Canada granted an NoC for the combination therapy, without any requirements for post-approval commitment studies. Further, we believe uncertainties expressed by pERC, can be alleviated through our network through the generation of real world data (prospectively) through use of the Canadian Kidney Cancer information system (CKCis).

1 About Stakeholder Feedback

pCODR invites eligible stakeholders to provide feedback and comments on the Initial Recommendation made by the pCODR Expert Review Committee (pERC). (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, pERC makes an Initial Recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The Initial Recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation. It should be noted that the Initial Recommendation may or may not change following a review of the feedback from stakeholders.

pERC welcomes comments and feedback from all eligible stakeholders with the expectation that even the most critical feedback be delivered respectfully and with civility.

A. Application of Early Conversion

The Stakeholder Feedback document poses two key questions:

1. **Does the stakeholder agree, agree in part, or disagree with the Initial Recommendation?**

   All eligible stakeholders are requested to indicate whether they agree, agree in part or disagrees with the Initial Recommendation, and to provide a rational for their response.

   Please note that if a stakeholder agrees, agrees in part or disagrees with the Initial Recommendation, the stakeholder can still support the recommendation proceeding to a Final Recommendation (i.e. early conversion).

2. **Does the stakeholder support the recommendation proceeding to a Final Recommendation ("early conversion")?**

   An efficient review process is one of pCODR's key guiding principles. If all eligible stakeholders support the Initial Recommendation proceeding to a Final Recommendation and that the criteria for early conversion as set out in the *pCODR Procedures* are met, the Final Recommendation will be posted on the CADTH website two (2) Business Days after the end of the feedback deadline date. This is called an "early conversion" of an Initial Recommendation to a Final Recommendation.

   For stakeholders who support early conversion, please note that if there are substantive comments on any of the key quadrants of the deliberative framework (e.g., differences in the interpretation of the evidence), the criteria for early conversion will be deemed to have **not** been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting. Please note that if any one of the eligible stakeholders does not support the Initial Recommendation proceeding to a Final pERC Recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the Initial Recommendation.

B. Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents. Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the Initial Recommendation. If the feedback can be addressed editorially this will done by the pCODR staff, in consultation with the pERC chair and pERC members, and may not require reconsideration at a subsequent pERC meeting.

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

2 Instructions for Providing Feedback

a) The following stakeholders are eligible to submit Feedback on the Initial Recommendation:

- The Submitter making the pCODR Submission, or the Manufacturer of the drug under review;
- Patient groups who have provided input on the drug submission;
- Registered clinician(s) who have provided input on the drug submission; and
- The Provincial Advisory Group (PAG)

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 *Stakeholder Feedback on pERC Initial Recommendation* can be downloaded from the pCODR section of the CADTH 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 Stakeholder 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.

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 provided to the pERC for their consideration.

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 program.

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

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

Note: CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback will be posted on the CADTH website (www.cadth.ca/pcodr). The submitted information in the feedback template will be made fully disclosable.

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Lenvatinib in combination with everolimus for Advanced Renal Cell Carcinoma (RCC)
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Group, Clinical Group):	Clinician
Organization Providing Feedback	Dr. Anil Kapoor (Urologic Surgeon) & Dr. Aly-Khan Lalani (Medical Oncologist) Juravinski Cancer Centre.

**The pCODR program 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 eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☐ agrees ☐ agrees in part ☒ disagree

We believe that the combination of lenvatinib + everolimus does significantly address an existing unmet need in this space as it allows for inhibition beyond just VEGFR targets, instead including FGFR and mTOR synergistic inhibition, which area major tumour escape mechanisms in RCC. Furthermore, we believe the randomized phase II data provides meaningful high-level evidence to form the basis of treatment and that

any potential remaining uncertainties can be dutifully addressed prospectively in a real world setting.

b) Please provide editorial feedback on the Initial Recommendation to aid in clarity. 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 #	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
p.1	pERC Recommendation	Para 2	pERC: "The Committee made this recommendation because it was not satisfied that there is a net clinical benefit of Lenvatinib in combination with everolimus compared with everolimus monotherapy" Response: We believe that the committee came to the incorrect conclusion of the net clinical benefit of lenvatinib + everolimus, based on the evidence, and based on the expert opinion of mRCC treating clinicians (Dr. Lalani and Dr. Kapoor were contributors to a clinician submission to pCODR). We also believe pERC should have highlighted that it made its recommendation in contradiction to the recommendation made by pCODR's own Clinical Guidance Panel report where it concluded: "…there is a net overall clinical benefit to lenvatinib/everolimus compared with everolimus monotherapy for the second-line (after 1 prior VEGF-targeted therapy) treatment of advanced and metastatic RCC based on one randomized controlled phase Ib/II trial (HOPE-205) that demonstrated a clinically meaningful and statistically significant benefit in response rate, PFS and OS for lenvatinib/everolimus compared with everolimus."

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder would support this Initial Recommendation proceeding to Final pERC Recommendation ("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

☐ Support conversion to Final Recommendation.

☒ Do not support conversion to Final Recommendation.

Recommendation does not require reconsideration by pERC.

Recommendation should be reconsidered by pERC.

Page #	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
p.3	Summary of pERC Deliberations	Para 2	Re: Magnitude of benefit (importance of PFS, ORR, and OS in this therapeutic area) pERC: "While the results of progression-free survival (PFS), the primary outcome of the trial, were statistically significant in favour of lenvatinib in combination with everolimus, pERC noted the limitations of using phase II trials to guide recommendations given the considerable uncertainty around the magnitude of the PFS benefit." Responses: - The Clinical Guidance Report (CGR) stated "the extent of clinical benefit from lenvatinib/everolimus, the overall magnitude of superiority in response rate, PFS and OS **clearly favors** the combination of lenvatinib/everolimus over everolimus alone." (p.18) - Our experience at the Juravinski Cancer Centre with this drug combination is supportive of the CGR conclusion. We have seen patients respond very well to this treatment and believe it will be an important and necessary addition to the treatment armamentarium for metastatic/advanced RCC.
p.3	Summary of pERC Recommendations	Para 2	pERC: "…it is feasible to conduct a Phase III RCT in this setting". Responses: As researchers involved in clinical trials for mRCC along with assessing and developing evidence for treatment consensus through the Kidney Cancer Research Network of Canada (KCRNC), we take this opportunity to point out for the benefit of pERC that there are unique considerations for trial design in this landscape of mRCC. Given the historically limited patient population availing of 2nd and 3rd line treatment in metastatic RCC, phase III trials are not always feasible. In this context, well designed, randomized phase II data can provide meaningful high-level evidence to form the basis of treatment options in various jurisdictions. Furthermore, in Canada, the Canadian Kidney Cancer information system (CKCis) provides an unparalleled opportunity to generate evidence prospectively to determine the extent of clinical benefit of new treatments. -We wish to also remind pERC that Health Canada reviewed HOPE-205 using the same rigorous criteria applied for phase III pivotal trials.
p.2	Summary of pERC Recommendations &	Para 1	pERC: "Given the availability of other treatments following progression on a VEGF-targeted therapy, pERC was uncertain whether Lenvatinib in combination with everolimus addresses an unmet need." Comments: Response: -pERC identifies that there is an unmet need pERC: "….there is a need for more effective and less toxic novel therapies, which overcome disease resistance, delay disease progression and improve

p.8	OVERALL CLINICAL BENEFIT	Para 4	OS." (p.8). The combination therapy of lenvatinib and everolimus, with distinct and synergistic mechanisms of action, would provide a meaningful options for patients in this unmet need. The Clinical Guidance Report confirms the need for additional treatment options: "Limited treatment options exist for patients with metastatic RCC who have failed first-line therapy. Axitinib and nivolumab are the only funded drugs available. These drugs have different toxicity profiles and are associated with a number of substantial side effects, including hypertension, fatigue, diarrhea, hand-foot syndrome or autoimmune syndromes, all of which can greatly impact a patient's quality of life, optimal administration of therapy and subsequent outcomes. Hence **there is an urgent need for better and additional treatment options in RCC**." -We believe that lenvatinib + everolimus does significantly address and existing unmet need in this space as it allows for inhibition beyond just VEGFR targets, including FGFR, a major tumour escape mechanism in RCC -importantly, lenvatinib is available in 4mg and 10mg capsules allowing physicians the most flexibility to optimize patient management. Multiple dosing modifications can be made without major compromises to treatment efficacy through incremental titrations or escalations. Lenvatinib's unique dosing possibilities ultimately afford physicians a powerful novel therapy for RCC patients to address existing unmet need.
p.3	Summary of pERC Recommendations		pERC: "pERC acknowledged that the CGP anticipated that, rather than replacing alternative therapies, lenvatinib in combination with everolimus would be used in case of contraindications to or tolerability concerns with treatments that are currently standard of care." <u>Responses</u>: In terms of place in the landscape of therapy that lenvatinib + everolimus would provide, we point out the clinical guidance panel review statement below: "However, given the available data of other targeted agents and the completely different mechanism of action of lenvatinib/everolimus there is no reason why patients pretreated with 1 prior TKI and immunotherapy should not respond to lenvatinib/everolimus." -We believe that lenvatinib + everolimus should be approved for second or third line therapy after 1 prior TKI or after TKI and immunotherapy. -Having three lines of therapy available for patients, is extremely important in this setting as some patients will not respond to existing available therapies

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Lenvatinib for Advanced Renal Cell Carcinoma (RCC)
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Group, Clinical Group):	Clinician
Organization Providing Feedback	Dr. Eric Winquist

**The pCODR program 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 eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☐ agrees ☐ agrees in part ☒ disagree

Please explain why the Stakeholder *agrees, agrees in part or disagrees with the Initial Recommendation. If the Stakeholder agrees in part or disagrees with the Initial Recommendation, please provide specific text from the recommendation and rational. Please also highlight the applicable pERC deliberative quadrants for each point of disagreement. The points are to be numbered in order of significance.*

b) Please provide editorial feedback on the Initial Recommendation to aid in clarity. 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
p.1	pERC Recommendation	Para 2, Line 1.	The initial pERC recommendation to not fund lenvatinib + everolimus for mRCC "..because it was not satisfied that there was a net clinical benefit of lenvatinib in combination with everolimus compared to everolimus monotherapy." is incongruent with the conclusions of the Clinical Guidance Panel which concluded: "… there is a net overall clinical benefit to lenvatinib/everolimus compared with everolimus monotherapy for the second-line…." I believe that pERC came to the wrong conclusion based on the evidence, and based on expert clinical experience with this drug. For clarity and transparency, pERC should make it explicitly clear that the Committee did not agree with the CGP and clinician experts who have experience treating patients with this novel drug combination.

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder would support this Initial Recommendation proceeding to Final pERC Recommendation ("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

☐	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.

If the eligible stakeholder does not support conversion to a Final Recommendation, please provide feedback on any issues not adequately addressed in the Initial Recommendation

based on any information provided by the Stakeholder 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 program.

Additionally, if the eligible stakeholder supports early conversion to a Final Recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, the criteria for early conversion will be deemed to have not been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
p.3	Summary of pERC Deliberations	Para 2	pERC has chosen to emphasize that the HOPE-205 RCT was a phase II clinical trial. However, all phase II trials are not the same, and this trial was randomized, reasonably powered, and chose a primary outcome measure (PFS) that is commonly used as a primary outcome in larger phase III cancer trials. The control arm of everolimus was standard of care at the time the trial was conducted, and the credibility of this control arm is confirmed by the ORR (6%) and PFS (5.5 months) with everolimus. These were very similar to those seen in the Checkmate-025 trial which led to pERC approval of nivolumab compared to an everolimus control arm (ORR 5% and PFS 4.4 months). The concordant improvements in ORR, PFS and OS observed in HOPE-205 might be exaggerated slightly by type I error but they are very unlikely to be qualitatively different. It is surprising that pERC views these results so differently from trials of similar sample size labelled “phase III” which are reported as positive for PFS but negative for OS with the latter attributed to post-progression contamination due to optional therapeutic crossover. Recommendation 10066 for the AURELIA RCT studying the addition of bevacizumab to chemotherapy for ovarian cancer is but one example of a positive pERC recommendation based on an RCT negative for OS. Unless clearly justified such inconsistency raises concerns about disease-based discrimination in decision-making.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
p.3-4	Summary of pERC Deliberations	Para 4	This paragraph discusses comparators to lenvatinib/everolimus. Only nivolumab, cabozantinib and everolimus are relevant to this discussion by direct comparison in RCTs. Cabozantinib is dismissed as irrelevant and unavailable. Nivolumab has been favorably recommended and funded across Canada. Unlike many solid tumors in adults, cytotoxic chemotherapy is ineffective in mRCC. As such, treatment options for patients who cannot receive nivolumab due to contraindication such as solid organ transplant or severe autoimmune disease are limited to everolimus, a much less effective drug. These patients deserve more effective treatment than everolimus monotherapy. Some mRCC patients present with rapidly progressing disease involving critical organs despite first-line TKI therapy. As these patients have "one shot" to respond, treatment associated with a high ORR is preferred. Certainly the HOPE-205 trial is adequately powered to unequivocally confirm a much higher ORR (43%) than either nivolumab (25%) or everolimus (6%) for such patients. My clinical experience with the combination has confirmed the high ORR reported. As well, the extremely high ORR seen with lenvatinib seen in iodine-refractory thyroid cancer (65% compared to 12% with sorafenib) suggests lenvatinib has unique activity for a TKI and that this is unlikely to be a chance or exaggerated phenomenon. Finally, there is high-level evidence supporting combined immunotherapy as first-line therapy for mRCC compared to monotherapy TKI and it is likely that pERC will deliberate on this soon. Although unstudied it seems unlikely that patients progressing despite IO agents will respond to second-line monotherapy with everolimus or TKI agents shown inferior to them in the first-line setting. Lenvatinib/everolimus may be a more active therapeutic option for consideration in such patients.

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p. 4	Summary of pERC Deliberations	Para 7	pERC has recommended approval of other drugs based on modelling of phase III trials with negative OS results, so this reasoning seems a bit disingenuous.
p. 4-5	Summary of pERC Deliberations	Para 8	Everolimus is soon to become a generic drug, and it is unclear if the effect of everolimus price reduction on estimates of cost-effectiveness was considered. Budget impact can be controlled at the provincial level by implementation of specific funding criteria and monitoring of compliance to these.

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