pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

Addendum: This is a revised Final Recommendation, which supersedes the March 7, 2013 Final Recommendation for this drug and indication. This revision was made as a result of a Request for Advice (RFA) from the pCODR Provincial Advisory Group (PAG), who submitted a question to the pERC regarding a clinical issue. Therefore, this revision does not address cost-effectiveness, patient values or adoption feasibility.

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

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is amended based on a Request for Advice question submitted by the Provincial Advisory Group (PAG) and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the previous Final Recommendation issued on March 7, 2013. The economic evaluation, patient values, and adoption feasibility, of the initial recommendation remain unchanged.

Drug: Axitinib (Inlyta) **Submitter's Funding Request:** For the treatment of patients with metastatic renal cell carcinoma (RCC) of clear cell histology after failure of prior systemic therapy with either a cytokine or the VEGFR-TKI sunitinib. **Request for Advice:** Is there evidence to fund axitinib as an alternative to everolimus for the second-line treatment of metastatic clear cell renal carcinoma?	
Submitted by: Pfizer Canada Inc.	**Manufactured by:** Pfizer Canada Inc.
NOC Date: July 12, 2012	**Submission Date:** August 16, 2012
Initial Recommendation: January 14, 2013	**Final Recommendation:** March 7, 2013 **Revised:** June 29, 2017

pERC RECOMMENDATION on REQUEST FOR ADVICE	Following a Request for Advice, pERC recommends reimbursement of axitinib (Inlyta) as a second-line treatment option for patients with metastatic RCC of clear cell histology after failure of prior systemic therapy with either a cytokine or vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR TKI) treatment. pERC made this recommendation because multiple sources of retrospective evidence demonstrated that there may not be a difference in clinical benefit (based on overall survival, progression-free survival, and safety) between axitinib and everolimus in patients with disease progression after previous sunitinib treatment. Furthermore, pERC considered that there is no randomized controlled trial (RCT) comparing the clinical benefit of axitinib with that of everolimus in this group of patients, and it is highly unlikely that there will be. Although these retrospective studies had several limitations, pERC was satisfied that the results from these multiple sources demonstrated consistent outcomes, and concluded that axitinib is a reasonable treatment alternative to everolimus as a second-line treatment for patients with metastatic RCC. pERC did not deliberate upon patient values, adoption feasibility, and cost-effectiveness of axitinib compared with everolimus, as the Request for Advice question submitted by the pCODR PAG was specific to the clinical issue. For detailed information about the patient values, adoption feasibility, and economic evaluation, please refer to: https://www.cadth.ca/sites/default/files/pcodr/pcodr-inlytamrcc-fn-rec.pdf
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing of Axitinib and Everolimus** While pERC did not deliberate upon the patient values, adoption feasibility, and cost-effectiveness of axitinib and everolimus, the Committee noted that the costs of using either axitinib or everolimus should be comparable. pERC also noted that, if flat pricing of different strengths is in place, there is the potential for cost differences between everolimus and axitinib treatment if alternative dosing schedules/dose reductions are used in practice.

SUMMARY OF pERC DELIBERATIONS ON REQUEST FOR ADVICE

On March 7, 2013, pERC issued a reimbursement recommendation for axitinib (Inlyta) for metastatic RCC. On April 18, 2017, the pCODR PAG submitted a Request for Advice for the following question:

- Is there evidence to fund axitinib as an alternative to everolimus for the second-line treatment of metastatic clear-cell renal carcinoma?

pERC noted that two phase III RCTs investigated axitinib and everolimus separately as second-line treatment options for metastatic RCC. The AXIS trial found that axitinib was more efficacious than sorafenib; the RECORD1 trial found that everolimus was more efficacious than placebo. pERC noted the similarity of the evidence for everolimus and axitinib as second-line treatment for metastatic RCC, but that uncertainty existed in the comparative effectiveness of the two agents, as no RCTs directly comparing the two agents were identified by the pCODR systematic review. Furthermore, pERC acknowledged input from the pCODR Clinical Guidance Panel (CGP) that it was highly unlikely that an RCT comparing the effectiveness of axitinib versus everolimus in this patient population would be conducted.

pERC noted that the pCODR systematic review included nine retrospective observational studies (four full publications and five abstracts) that reported consistent results (i.e., overall survival and progression-free survival) to suggest that there is no statistically significant difference in the effectiveness of axitinib versus everolimus. pERC acknowledged the inherent limitations of retrospective observational data, and the limited reporting of study methodology in the included abstracts; however, the Committee felt that the consistency of the totality of the evidence mitigated some of the concerns of these statistical limitations. In the absence of safety data from the available studies, pERC noted the opinion of the CGP that, while there are differences in the toxicity of everolimus and axitinib, both agents have acceptable and manageable toxicity profiles. Therefore, pERC concluded that axitinib is a reasonable alternative to everolimus in patients with metastatic RCC.

In addition, pERC discussed the stakeholder input provided by the submitters of the original axitinib submission, Pfizer Canada Inc. and Kidney Cancer Canada (KCC), who provided patient input on the original axitinib submission. KCC provided data from its Canadian Kidney Cancer Information System, which is a database of Canadian patients with kidney cancer that tracks kidney cancer treatment practice in Canada. pERC noted that, despite some limitations, the data from its database supported the results of the systematic review. pERC also remarked that KCC's input was valuable in noting the Canadian experience for metastatic RCC. Pfizer Canada Inc. provided evidence from a match-adjusted indirect treatment comparison (ITC) of axitinib versus everolimus. pERC noted that similar studies were identified in the pCODR systematic review, and that the comparison provided by Pfizer Canada Inc. reported similar results.

pERC did not deliberate upon the patient values, adoption feasibility, and cost-effectiveness of axitinib and everolimus, as the pCODR PAG Request for Advice question was specifically regarding the clinical issue. However, pERC noted that the costs of using either axitinib or everolimus should be comparable. pERC also noted that, if flat pricing of different strengths is in place, there is the potential for cost differences between everolimus and axitinib treatment if alternative dosing schedules/dose reductions are used in practice.

CONTEXT FOR REQUEST FOR ADVICE

PAG is seeking advice on the reimbursement of axitinib as an alternative to everolimus for the second-line treatment of metastatic clear cell renal carcinoma, rather than only for patients who are intolerant to or have contraindications to everolimus. At the time of the March 7, 2013 pERC Final Recommendation, there were no trials directly comparing the clinical effectiveness of axitinib with that of everolimus.

The interpretation of the March 2013 pERC recommendation and the resulting reimbursement criteria differ among the provinces. In some provinces, patients and their oncologist can choose between everolimus or axitinib, while in others, there must be a trial of everolimus prior to requesting funding for axitinib.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon the following to address the Provincial Advisory Group's (PAG's) Request for Advice:

- A pCODR systematic review
- Input from one patient advocacy group (Kidney Cancer Canada [KCC])
- Input from the manufacturer of axitinib (Inlyta) (Pfizer Canada Inc.)

The March 7, 2013, pERC Final Recommendation recommended funding axitinib (Inlyta) as a second-line treatment in patients with metastatic clear cell renal carcinoma who, based on the mutual assessment of the treating physician and the patient, are unable to tolerate the ongoing use of an effective dose of everolimus, or who have a contraindication to everolimus. The pCODR PAG Request for Advice was received on April 10, 2017:

- Is there evidence to reimburse axitinib as an alternative to everolimus for the second-line treatment of metastatic clear cell renal cell carcinoma?

CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the efficacy and safety of axitinib on patient outcomes compared with everolimus in the second-line treatment of patients with advanced or metastatic renal cell carcinoma (RCC) after failure of prior systemic therapy.

Studies included: nine retrospective observational studies

The pCODR systematic review included nine retrospective observational studies, of which four were fully published and five were abstract-only publications. The majority of included studies were retrospective chart reviews, with the exception of one match-adjusted indirect treatment comparison (ITC), one simulated treatment comparison, and one ITC.

One study reported that patients on axitinib had a higher rate of dose increase (13.2%) compared with those on everolimus (1.0%), and that patients on everolimus had a higher rate of dose decrease (12.1%) compared with those on axitinib (5.5%).

pERC discussed the retrospective observational studies and noted several limitations for each. While the Committee had concerns regarding the potential for bias in the ITCs, pERC felt that the consistency of results between all included studies was notable.

Patient populations: Majority of patients received prior sunitinib

A total of 389 patients (53.8%) were sunitinib refractory in the AXIS trial (which compared axitinib with sorafenib), 56 patients (10.9%) were sunitinib refractory in the RECORD-1 trial (which compared everolimus with placebo), and 415 patients (63.1%) were sunitinib refractory in the METEOR trial (which compared everolimus to cabozantanib). These trials) trials were used for matching in the ITCs, but the number of patients selected from each trial to be included in each of the ITCs was varied (see Table 4 of the pCODR Request for Advice Clinical Guidance Report).

For the retrospective chart reviews, patients included were 18 years or older and eligible for second-line targeted therapy after failure of first-line tyrosine kinase inhibitor (TKI) targeted therapy.

Key efficacy results: Progression-free survival and overall survival

Of the included full publications, two studies conducted ITCs. In Sherman et al (2015), the progression-free survival (PFS) for everolimus was 4.7 months (95% confidence interval [CI], 3.5 to 10.6); the PFS for axitinib was 4.8 months (95% CI, 4.5 to 6.4). Dranitsaris et al (2013) reported the hazard ratio (HR) for PFS as inconclusive, at 1.32 (95% credible interval [CrI], 0.88 to 2.0).

In 2012 and 2016, Proskorovsky et al conducted two different ITCs. The first was a simulated treatment comparison that showed median overall survival (OS) to be 15.2 months for axitinib and 10.6 months for everolimus, with PFSs of 5.1 months and 3.6 months, respectively. In 2016, a match-adjusted ITC was conducted that showed a median OS of 16.5 months (confidence interval [CI], 14.7 to 18.8) for everolimus and 23.8 months (CI, 15.7 to non-estimable [NE]) for axitinib, with a HR of 0.64 (CI, 0.45 to 0.91). The median PFS for the match-adjusted ITC was 3.7 months (CI, 1.9 to 4.2) and 7.8 months (CI, 6.3 to 13.9) for everolimus and axitinib, respectively, with a HR of 0.48 (CI, 0.32 to 0.73).

Of the included fully published retrospective chart reviews, Vogelzang et al (2016) reported OS rates at 12 months of 83% (95% CI, 74% to 89%) for axitinib and 80% (95% CI, 75% to 84%) for everolimus, with a HR of 1.02 (95% CI, 0.67 to 1.55) before adjusting and HR of 1.16 (95% CI, 0.74 to 1.82) after adjusting. The PFS at 12 months was 56% (95% CI, 47% to 65%) and 60% (95% CI, 54% to 65%) for axitinib and everolimus, respectively. The unadjusted HR for PFS was 1.07 (95% CI, 0.74 to 1.84) and the adjusted HR was 1.16 (95% CI, 0.55 to 1.82). Pal et al (2016), also looked at the comparative efficacy of everolimus versus axitinib; the adjusted HR for PFS was 1.16 (95% CI, 0.73 to 1.82).

Of the five retrospective chart review abstracts, median OS ranged from 8.5 months to 23 months for everolimus and 9.4 months to 23.5 months for axitinib. Median PFS for everolimus ranged from 4.7 months to 5.3 months; median PFS for axitinib was 6.5 months to 7.7 months. In Arranz-Arija et al (2015), the one-year OS was reported at 40.2% (29% to 53%) for everolimus and 32.6% (8% to 56%) for axitinib.

Though pERC acknowledged potential issues with the methodologies and inherent biases associated with the retrospective observational study results, pERC noted the consistency of the reported results.

Quality of life

Quality of life was not reported in any of the publications and abstracts.

Quality of life data were also not included in either of the stakeholder inputs from the manufacturer or patient advocacy group.

Harms outcomes

No harms outcomes were identified in the included published studies. However, adverse event information was provided by KCC as part of its stakeholder input.

Limitations: No direct comparison with everolimus and no ongoing trials

The main limitation identified by pERC is that there are no randomized controlled trials (RCTs) directly comparing axitinib with everolimus. pERC also noted that there are no planned or ongoing trials that will do so. pERC also discussed the inherent limitations of the retrospective chart reviews and the ITCs between axitinib and everolimus; however, the Committee concluded that the consistency of the totality of evidence gave them confidence in their conclusion that axitinib is a reasonable alternative to everolimus.

Comparator information: Uncertainty in results of indirect comparisons

In the absence of trials directly comparing axitinib with everolimus, pERC discussed observational information provided in the pCODR Clinical Guidance Report on axitinib versus everolimus and the limitations of ITCs as well as biases associated with retrospective chart reviews. pERC noted that because of differences in the study populations and study designs of RECORD-1 and METEOR compared with the AXIS study — and the lack of a common control group between the studies — the results of the ITC would have a number of limitations and be extremely uncertain. However, pERC also noted that the consistency in the direction of results between the retrospective chart reviews and ITCs was indicative of likely similar effectiveness between axitinib and everolimus. Furthermore, pERC noted that the limited methodological details provided in the included abstracts is not sufficient for an adequate critical appraisal.

Need: Inconsistency between funding criteria and the need for alternatives to everolimus

pERC considered that, due to the interpretation of the original March 2013 pERC recommendation, some provinces do not have specific criteria guiding treatment selection between everolimus and axitinib; however, some require that patients have a contraindication/intolerance to everolimus prior to using axitinib.

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. Maureen Trudeau, Oncologist (Chair)
Dr. Paul Hoskins, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
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
Dr. Marianne Taylor, Oncologist
Danica Wasney, Pharmacist

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

- Dr. Allan Grill, Dr. Scott Berry, Dr. Matt Cheung, and Jo Nanson, who were absent for the meeting.
- Dr. Marianne Taylor who was excluded from voting due a conflict of interest

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 Request for Advice of axitinib (Inlyta) for metastatic renal cell carcinoma, through their declarations, six members had a real, potential, or perceived conflict. Based on the application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

pERC is provided with a *pCODR Request for Advice Report*, as well as with the original stakeholder submissions, to inform its deliberations.

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*. There was no non-disclosable information in this recommendation document.

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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