pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

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 reimbursement 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 based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Lenvatinib (Lenvima) **Submitted Reimbursement Request:** In combination with everolimus for the treatment of patients with advanced or metastatic, clear-cell renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.	
Submitted By: Eisai Limited	**Manufactured By:** Eisai Limited
NOC Date: September 13, 2017	**Submission Date:** June 8, 2018
Initial Recommendation: November 1, 2018	**Final Recommendation:** January 4, 2019

Approximate Per-Patient Drug Costs, per Month (28 Days)	Lenvatinib plus everolimus costs $8,896.00 per 28-day drug cycle. At the recommended dose of 18 mg once daily (1 X 10mg, 2 X 4mg capsules), lenvatinib costs: • $8.14 per mg or $732.86 per unit (5-day blister card) • $146.57 per day

pERC RECOMMENDATION

pERC does not recommend reimbursement of lenvatinib in combination with everolimus for the treatment of patients with advanced or metastatic, clear-cell renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

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. While pERC acknowledged that lenvatinib in combination with everolimus produces some anti-tumour activity, the Committee noted that there was a high level of uncertainty around the magnitude of the progression-free survival (PFS) and overall survival (OS) benefits given the limitations in the evidence from the available phase II clinical trial. pERC also noted a lack of quality of life (QoL) data. Furthermore, the Committee was unable to determine how lenvatinib in combination with everolimus compares with other relevant treatment options given the lack of robust comparative data on outcomes important to decision-making, such as OS, PFS, and QoL. 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.

pERC noted that lenvatinib in combination with everolimus aligned with patient values of potentially delaying disease progression and offering an

	additional treatment choice. pERC could not draw a conclusion on the cost-effectiveness of lenvatinib in combination with everolimus compared with everolimus monotherapy, axitinib, or nivolumab due to the uncertainty in the available clinical data.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC considered that it is possible to conduct a phase III randomized controlled trial (RCT) in the requested reimbursement patient population. pERC noted that new clinical data comparing lenvatinib in combination with everolimus with currently available treatments in Canada for patients with advanced or metastatic, clear-cell RCC following one prior VEGF-targeted therapy could form the basis of a resubmission to pCODR if comparative efficacy data important to decision-making were provided.

SUMMARY OF pERC DELIBERATIONS

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2017, there were 6,600 new cases and 1,900 deaths related to kidney cancer. About 90% of kidney cancers are RCCs; 80% of all RCCs are of clear-cell histology, and 20% are classified as non-clear cell cancers. In localized stages of RCCs, survival rates range from 70% to 90%, but drop to 50% to 60% for patients with more extensive tumours. The current standard of care for patients with advanced or metastatic, clear-cell RCC who have had one prior VEGF-targeted therapy includes nivolumab, which is the most commonly used therapy, axitinib, or everolimus. Despite current treatment options, long-term survival and cure are still rare for patients with metastatic RCC, particularly in the second-line setting, with less than 10% of metastatic patients surviving for five years or longer. pERC agreed that there is a need for more effective and less toxic therapies that overcome disease resistance, delay disease progression, and improve OS.

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

pERC thoroughly reviewed feedback received from all stakeholders and, while many perspectives were considered, the Committee decided to maintain its Initial Recommendation. pERC deliberated on the results of one multi-centre, open-label, phase Ib/II RCT (HOPE-205). The phase Ib portion evaluated the maximum tolerable dose of lenvatinib in combination with everolimus, while the phase II portion evaluated the efficacy and safety of lenvatinib in combination with everolimus (arm A) compared with lenvatinib monotherapy (arm B) and everolimus monotherapy (arm C) in patients with advanced or metastatic, clear-cell RCC following one prior VEGF-targeted therapy. pERC only discussed the evidence comparing arm A (lenvatinib in combination with everolimus) and arm C (everolimus monotherapy) because lenvatinib monotherapy (arm B) is currently not a relevant treatment option in Canada and is beyond the scope of this review. While the results of 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 funding recommendations given the considerable uncertainty around the magnitude of the PFS benefit. Specifically, the Committee discussed the small sample size of the study, which was a result of a high one-sided alpha level of 0.15 and a low statistical power of 70%; the combination of which leads to an increased risk of a false-positive result.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed the feedback provided by the submitter suggesting that the risk of a false-positive result given the actual data from HOPE-205 is extremely low and well within the accepted confidence intervals, confirming the efficacy of lenvatinib in combination with everolimus in the HOPE-205 trial. Furthermore, the submitter also provided feedback that a Bonferroni correction was applied to adjust for multiplicity in the primary outcome to maintain the type I error rate at 0.05. pERC agreed with the pCODR Methods Team and with the submitter that PFS was statistically significant based on a significance level of 0.05 (two-sided) and that by applying a Bonferroni correction to adjust for multiple comparisons of the PFS results, there was no increased risk of a type I error for the primary outcome. However, pERC noted that the results of the secondary end points and subgroup analyses of PFS were still at risk of type I error because of the lack of multiplicity adjustment. pERC further discussed that there is a distinction between the type I error rate and a general risk of a false-positive finding, the latter of which relates to the limitation of the study design. By using a one-sided alpha of 15%, the calculated sample size was less than if a smaller alpha had been selected (e.g., a one-sided alpha of 10% or two-sided alpha of 5%). It is possible that the hazard ratio and statistical significance observed in this small cohort of patients may represent a sample of outliers in the population and not represent the treatment effect expected in the full population. As such, it is possible that the observed treatment effect may be a false-positive result or that the true treatment effect may be smaller than what was reported in this study. Therefore, pERC agreed that while there was no increased risk of type I error rate in the primary outcome, this phase II trial could be more likely to produce a false-positive result than trials of larger sample size.

Further, pERC noted that the HOPE-205 trial was not powered to detect a statistically significant OS benefit and was unable to draw firm conclusions on the OS results observed in the trial. In addition, pERC discussed that phase II trials are mainly hypothesis-generating and their intent is to determine whether or

not there is sufficient promise to proceed to a phase III confirmatory trial. pERC was unsure about whether the results observed in this phase II trial will translate into positive phase III trials or into real-world clinical practice.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter and registered clinicians noting that the overall magnitude of superiority in objective response rate and PFS demonstrated in the HOPE-205 trial clearly favours lenvatinib in combination with everolimus over everolimus alone. pERC discussed the response provided by the pCODR Clinical Guidance Panel (CGP) in the pCODR Clinical Guidance Report (CGR) comparing the activity of lenvatinib in combination with everolimus in this phase II trial with the activity of other currently used and upcoming agents assessed in phase III trials. While pERC acknowledged the CGP's response, pERC reiterated that it is important to note that the primary objective of phase II (randomized or non-randomized) trials is to document the safety outcomes and investigate if the estimate of effect for a new drug is large enough to use it in confirmatory phase III trials. The purpose of phase II trials is not to provide definitive estimates of efficacy. In addition, pERC reiterated that the sample size of this submitted phase II trial was small and more likely to produce a false-positive result than trials of larger sample sizes. Therefore, pERC remained uncertain whether the results observed in this phase II trial will translate into positive phase III trials or into benefit in real-world clinical practice.

pERC noted that it is feasible to conduct a phase III RCT in this setting because previous pCODR reviews in this line of therapy had been based on phase III RCTs.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter, the registered clinicians, and the patient advocacy group noting that there are few head-to-head comparisons between currently approved drugs in the second-line setting, and that, given the historically limited patient population available for second- and third-line treatment in metastatic RCC, phase III trials are not always feasible. pERC agreed with the response provided by the CGP in the CGR, noting that, although it is challenging to perform randomized trials in the second- and third-line setting of metastatic RCC, at least five to six randomized trials have been successfully performed. An additional challenge is the constantly changing therapeutic landscape in first- and second-line RCC due to the introduction of novel therapies. While pERC acknowledged there are challenges with conducting large randomized trials in this setting, the Committee reiterated that it is feasible to conduct a phase III RCT versus standard of care in patients with advanced or metastatic, clear-cell RCC following one prior VEGF-targeted therapy, as previous pCODR reviews in this line of therapy had been based on phase III RCTs. Clinical data from a phase III RCT could provide clarity on the comparative effectiveness of lenvatinib in combination with everolimus compared with standard of care on outcomes important to decision-making, such as PFS, OS, and QoL.

pERC noted that the impact of lenvatinib in combination with everolimus on patients' QoL is unknown as it was not measured in the trial. pERC further discussed that lenvatinib in combination with everolimus increased toxicity compared with everolimus monotherapy, albeit in line with the known side effect profile of each individual agent. The incidence of grade 3 or 4 treatment-emergent adverse events (TEAEs) was higher for lenvatinib in combination with everolimus, which was mainly driven by the following grade 3 TEAEs: diarrhea, hypertension, fatigue, anemia, and vomiting. There were more serious adverse events as well as more patients who discontinued treatment due to adverse events in the lenvatinib and everolimus combination arm than in the everolimus monotherapy arm. Overall, pERC agreed with the CGP as well as with the registered clinicians providing input, that although lenvatinib in combination with everolimus has more toxicity than everolimus monotherapy, adverse events were overall acceptable and manageable.

Furthermore, pERC discussed other currently relevant treatment options in the requested patient population. While everolimus monotherapy may have been an appropriate comparator at the time of the HOPE-205 design, pERC noted that nivolumab and axitinib are more relevant comparators currently. 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.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter, registered clinicians, and the patient group that suggested that there is an urgent need for better and additional treatment options in RCC. pERC reiterated that there is still an unmet need for further treatment options for this patient population. However, given the high level of uncertainty in the results from the available phase II trial and the lack of robust comparative data with respect to outcomes

important to decision-making, the Committee could not confidently conclude that lenvatinib in combination with everolimus addresses the need for more effective treatment options in this setting.

In the absence of a direct comparison of lenvatinib in combination with everolimus with other relevant treatment options, pERC considered the results of a submitted indirect treatment comparison (ITC) that included comparisons of lenvatinib in combination with everolimus against cabozantinib, nivolumab, and everolimus monotherapy. pERC noted that cabozantinib was not regarded as a relevant comparator at the time of this pCODR review, as it is currently not publicly funded in any participating jurisdiction and is currently under review with pCODR. pERC agreed with the Methods Team that, given the limitations in the underlying data, overlapping credible intervals (i.e., statistical non-significance), limitations arising from the lack of closed loops in the network, the limited number of studies for each treatment comparison (one study per comparison), and lack of indirect comparisons for safety data and other efficacy outcomes (e.g., objective response rate, QoL), the comparative effectiveness of lenvatinib in combination with everolimus versus nivolumab remained uncertain.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter that stated that the ITC was appropriate for decision-making and performed based on the best available evidence and well-accepted methods, including appropriate handling (through fractional polynomials) of survival data that did not support the proportional hazard assumption. The submitter further suggested that overlapping credible intervals are a common finding in ITCs and therefore not a limitation, and that patient characteristics across trials were generally similar, suggesting a low risk of bias due to between-trial heterogeneity in the ITC results. pERC discussed the response provided by the pCODR Methods Team in the CGR, agreeing that potential limitations of the available evidence were brought to the reader's attention, with no specific concerns regarding the appropriateness of ITC methods (design and analysis). pERC further noted that the overlapping credible intervals were not listed as a methodological limitation of the ITC but rather indicated a lack of statistical significance between the comparators of interest, and that this was highlighted as a point to consider when interpreting the ITC results. pERC concluded that the fact that an ITC is based on well-accepted methods does not necessarily imply that the available evidence is sufficiently conclusive.

In addition, pERC noted that axitinib was not included in the submitted ITC due to concerns with transitivity (different eligibility criteria). Therefore, the Committee was unable to determine how lenvatinib plus everolimus compared with nivolumab or axitinib given the lack of robust comparative data on outcomes important to decision-making, such as OS, PFS, safety, and QoL.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter that noted that the ITC between lenvatinib in combination with everolimus and axitinib is appropriate as the assumption that axitinib and everolimus perform similarly is supported by The National Institute for Health and Care Excellence and the CGP. pERC discussed the response provided by the pCODR Methods Team in the CGR that confirmed that the ITC reported in the CGR (updated network that excludes sorafenib as an irrelevant comparator) does not include axitinib due to lack of evidence. In response to the submitter's feedback, the CGP confirmed that the assumption of equal effect sizes for axitinib and everolimus sounded clinically reasonable. While pERC acknowledged the CGP's perspective, the Committee agreed with the pCODR Methods Team that the validity of an ITC is based on several fundamental methodological assumptions; without including the trial of axitinib in the ITC, these assumptions cannot be fully and directly explored, thus leaving uncertain the relative effectiveness of lenvatinib in combination with everolimus compared with axitinib.

Therefore, pERC was not satisfied that there is a net clinical benefit to lenvatinib in combination with everolimus compared with everolimus monotherapy in patients with advanced or metastatic, clear-cell RCC following one prior VEGF-targeted therapy. While pERC acknowledged the CGP's positive conclusion, the need for more effective treatment options with different toxicity profile, and that lenvatinib in combination with everolimus produces some anti-tumour activity, the Committee noted that there was a high level of uncertainty around the magnitude of the PFS and OS benefits given the limitations in the evidence from the available phase II clinical trial. Furthermore, pERC was unable to determine how lenvatinib in combination with everolimus compares with the current standard of care therapies in Canada given the lack of robust comparative data with respect to outcomes important to decision-making such as OS, PFS, safety, and QoL. Given that it is feasible to conduct phase III RCTs in the present setting, pERC noted that data from a phase III RCT could provide clarity on the comparative effectiveness of lenvatinib in combination with everolimus compared with standard of care on outcomes important to decision-making, such as PFS, OS, and QoL.

Upon reconsideration, pERC discussed feedback from the submitter that the US FDA, the European Medicines Agency, Health Canada, and other global regulatory agencies had approved the use of

lenvatinib in combination with everolimus in the present setting. pERC noted that the role of regulatory agencies in providing approval is limited to determining whether the benefit-risk ratio is favourable. pERC stressed that its role as a health technology assessment body is broader than the previously mentioned bodies in that it examines the comparative effectiveness of different treatment strategies, looking at multiple dimensions while aiming to provide a balance between the values, needs, preferences, and perspectives of patients and those of society.

Also, upon reconsideration, pERC discussed feedback from the registered clinicians that suggested that their clinical experience is supportive of the CGP's conclusion and patients respond very well to lenvatinib in combination with everolimus. However, pERC reiterated that its mandate is to make evidence-based recommendations, and that there was a high level of uncertainty around the magnitude of the PFS and OS benefits of lenvatinib in combination with everolimus given the limitations in the evidence from the available phase II clinical trial.

pERC deliberated on input from one patient advocacy group. pERC noted that the majority of patients who have experience with lenvatinib in combination with everolimus considered this combination to be a very effective therapy against their kidney cancer, affording them a high QoL with side effects that were well tolerated. Most patients agreed that the benefits of the lenvatinib combination outweighed the experience of the side effects. pERC considered that patients value having access to more effective therapies that offer better long-term control of disease, overcome drug resistance, and offer patients more choice for drug treatments based on side effects and contraindications. pERC concluded that compared with everolimus monotherapy, the lenvatinib combination offers an additional treatment option with the potential to delay disease progression and therefore aligned with patient values, but the magnitude of the benefit is uncertain compared with everolimus monotherapy or other currently available treatment options. Upon reconsideration, pERC discussed feedback from the patient advocacy group emphasizing that one patient was interviewed in depth about his experience with lenvatinib in combination with everolimus and reported significant improvement of his disease and QoL. While the Committee acknowledged the importance of understanding the patient experience, pERC reiterated that there was a high level of uncertainty around the magnitude of the benefit compared with everolimus monotherapy or other currently available treatment options given the limitations in the evidence from the available phase II clinical trial.

pERC deliberated on the cost-effectiveness of lenvatinib in combination with everolimus compared with everolimus monotherapy, nivolumab, or axitinib for patients with advanced or metastatic, clear-cell RCC who have had one prior VEGF-targeted therapy. pERC agreed that the estimates of incremental effectiveness are largely based on a key clinical assumption that the efficacy results observed in the HOPE-205 trial and the submitted ITC translate into real and meaningful improvements in PFS and OS in the lenvatinib combination compared with other currently available therapies. Given the Committee's lack of confidence in the treatment effect estimates for lenvatinib in combination with everolimus due to the limitations in the evidence from the available phase II clinical trial and the ITC analysis, and the inability of the economic model to account for the resulting uncertainty in the parameter estimates, pERC agreed that the clinical effectiveness estimates could not be used to inform credible incremental-cost-effectiveness ratio (ICER) estimates.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter acknowledging that the 20% distribution around the OS and PFS curves in the economic model was set arbitrarily. As a consequence, the submitter provided a revised analysis to pCODR to more appropriately account for the uncertainty of efficacy inputs by incorporating the uncertainty estimated in the fractional polynomial ITC through 95% credible intervals fitted within the Bayesian ITC. The 95% credible intervals are calculated based on the inputs in the ITC and are not arbitrarily chosen. Furthermore, the submitter suggested that the revised results, based on the incorporation of these 95% credible intervals, would enable the estimation of the currently undefined upper bound ICER. pERC discussed the response provided by the pCODR Economic Guidance Panel (EGP) in the pCODR EGR that the revised analysis more appropriately captures the uncertainty around the efficacy inputs. However, the 95% credible intervals further highlight the uncertainty with the data from the ITC, demonstrating that the intervals extend beyond the "+/–20%" originally submitted. Despite the provision of a revised model with improved handling of uncertainty around effectiveness, the EGP reiterated that there is still a high level of underlying uncertainty in the data due to the lack of statistical significance in the efficacy data as observed by overlapping credible intervals. Therefore, pERC agreed with the EGP that no change is required in the original EGP's best-case reanalyses.

Therefore, pERC could not draw a conclusion on the cost-effectiveness and could not determine the ICER of lenvatinib in combination with everolimus compared with everolimus monotherapy, nivolumab, or axitinib for the treatment of patients with advanced or metastatic, clear-cell RCC following one prior VEGF-targeted therapy.

pERC considered the feasibility of implementing a reimbursement recommendation for the lenvatinib combination for the treatment of patients with advanced or metastatic, clear-cell RCC following one prior VEGF-targeted therapy. pERC discussed the Provincial Advisory Group's request for clarity on sequencing of treatments, on whether treatment with single agent lenvatinib or single agent everolimus is appropriate in patients with intolerance to lenvatinib in combination with everolimus and whether the results of the HOPE-205 trial could be generalized to certain patient subgroups not included in the HOPE-205 trial. pERC also considered that lenvatinib in combination with everolimus is a high-cost regimen and that the submitted Canada-wide budget impact was likely underestimated. pERC noted that according to the submitted base case introducing lenvatinib in combination with everolimus to the market resulted in savings over three years. pERC discussed that possible reasons for the savings could be the treatment duration and acquisition cost of nivolumab. pERC noted that the submitted total three-year budget impact of lenvatinib in combination with everolimus increases by about 4.5% (rendering the treatment-funded scenario more expensive and eliminating any savings) if the treatment duration of nivolumab is decreased from 7 to 5.5 months, and decreases by about 29% (rendering the treatment-funded scenario cheaper and increasing savings) if the treatment duration of nivolumab is increased from seven to 16 months. Further, increasing the proportion of patients eligible to receive lenvatinib in combination with everolimus through publicly funded drug plans from 49% to 95%, decreases the total three-year budget impact of lenvatinib in combination with everolimus by about 0.5% (rendering the treatment-funded scenario cheaper and increasing savings). pERC noted that a key limitation of the budget impact analysis is the inclusion of those younger than 18 years old in the population estimates, as the funding aligns with the patient population in the HOPE 205 trial, which limited eligibility to patients ≥ 18 years of age. Overall, the Committee concluded that the budget impact is likely underestimated.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided 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, Kidney Cancer Canada (KCC)
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, KCC
- Registered clinicians
- PAG
- The submitter, Eisai Limited.

The pERC Initial Recommendation was to not recommend reimbursement of lenvatinib in combination with everolimus for the treatment of patients with advanced or metastatic, clear-cell renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

Feedback on the pERC Initial Recommendation indicated that the PAG agreed with the Initial Recommendation. The patient advocacy group, registered clinicians, and the submitter disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the efficacy and safety of lenvatinib (Lenvima) in combination with everolimus compared with everolimus monotherapy in patients with advanced or metastatic, clear-cell renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

Studies included: One open-label randomized phase Ib/II trial

The pCODR systematic review included one multi-centre, open-label phase Ib/phase II randomized controlled trial (RCT), the HOPE-205 trial, comparing the combination of lenvatinib and everolimus (arm A) with lenvatinib monotherapy (arm B) and everolimus monotherapy (arm C) in patients with advanced or metastatic RCC following one VEGF-targeted therapy. During phase Ib, dose escalation was performed to determine the maximum tolerated dose of lenvatinib in combination with everolimus. This pCODR review reported on arms A and C of the phase II design, as single agent lenvatinib (arm B) is currently not a treatment option in Canada for second-line advanced or metastatic RCC and was therefore beyond the scope of the review.

A total of 153 patients were randomized (1:1:1 ratio) in HOPE-205, with 51 assigned to lenvatinib in combination with everolimus and 50 to everolimus monotherapy. Patients in the combination group were treated with oral lenvatinib (18 mg/day; one 10 mg capsule and two 4 mg capsules) in combination with oral everolimus (5 mg/day; one 5 mg tablet). Patients in the everolimus monotherapy arm received oral everolimus (10 mg/day; two 5 mg tablets). Patients were to remain on study treatment until disease progression, withdrawal of consent, or the development of unacceptable toxicity.

Median duration of lenvatinib exposure was 7.6 months (range 0.7 to 22.6) for patients receiving lenvatinib in combination with everolimus. The median daily dose of everolimus was 4.7 mg/day (94% of the intended dose) per patient assigned to lenvatinib + everolimus, and 9.7 mg/day (97% of the intended dose) per patient assigned to everolimus monotherapy. The median daily dose of lenvatinib was 13·6 mg/day (75% of the intended dose) per patient assigned lenvatinib + everolimus.

To manage treatment-related toxicities in the lenvatinib + everolimus and lenvatinib monotherapy arms, dose reduction and interruption were allowed in accordance with protocol pre-specified dose adjustment instructions.

To be eligible for enrolment in the study, patients had to be 18 years of age or older; to have documented unresectable or advanced RCC; to have a histological or cytological confirmation of predominant clear-cell carcinoma; to have been treated with one prior VEGF-targeted agent (e.g., sunitinib, sorafenib, pazopanib, bevacizumab, axitinib, vatalanib, AV951/tivozanib); and to have a radiographic evidence of disease progression according to modified Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) during or within nine months of stopping VEGF-targeted therapy. The inclusion criteria also required a minimum of one measurable lesion according to RECIST criteria, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate renal, bone marrow, blood coagulation, liver, and cardiac function.

Patient populations: Median age 61 years, all patients received previous VEGF-target therapy, number of metastases not balanced across groups

Overall, the baseline demographic and disease characteristics were well balanced between the study arms, except for the number of metastases: 35% of patients in the lenvatinib + everolimus arm had one metastasis, when compared with 10% of those in the everolimus arm. On the other hand, a higher percentage of patients in the everolimus arm had three or more metastases (60% versus 35% in the lenvatinib + everolimus arms). The median age was 61 years, ranging from 37 to 79 years between the three study arms. The majority of study patients were 65 years of age or younger (65%), white (97%), and male (73%). All patients received one previous VEGF-targeted therapy, with the most frequent agent being sunitinib (71% and 56% in the lenvatinib + everolimus and everolimus arms, respectively) and pazopanib (18% and 26% in the lenvatinib + everolimus and everolimus arms, respectively). The duration of previous VEGF-targeted therapies was slightly higher in the lenvatinib + everolimus arm (9.8 month; 95% CI, 2.0 to 66.2) than that in the everolimus arm (8.9; 95% CI, 1.6 to 57.8). The proportion of patients who underwent previous radiotherapy was 12 % in the lenvatinib + everolimus arm, and 22% in the everolimus arm. A small portion of patients had received prior treatment with checkpoint inhibitors (anti-PD1) (2% and 4% in the lenvatinib/everolimus and everolimus arm, respectively).

Key efficacy results: Considerable uncertainty around the magnitude of the PFS and OS benefits due to limitations of the phase II design of the trial

The primary outcome of the study was progression-free survival (PFS) as assessed by the investigator. Secondary outcomes included: overall survival (OS), objective response rate (ORR), disease control rate, clinical benefit rate, and safety. The trial was designed to have 70% power to detect a hazard ratio (HR) of 0.67 for PFS at a one-sided significance level (α) of 0.15. HOPE-205 was not powered to detect a significance difference in OS between the study arms. No adjustments were made for multiplicity introduced by analyzing multiple secondary end points or subgroup analyses of PFS.

As of June 13, 2014, data cut-off, 26/51 (51%) patients treated with lenvatinib + everolimus had disease progression (as assessed by the investigator) or died, as compared with 37/50 (74%) patients treated with everolimus. The median PFS was 14.6 months (95% CI, 5.9 to 20.1) for the lenvatinib + everolimus arm and 5.5 months (95% CI, 3.5 to 7.1) in the everolimus arm (stratified HR = 0.401, 95% CI, 0.239 to 0.675; *P* = 0.0005). Additional sensitivity analyses (with ECOG performance score as an additional stratum in the stratified Cox regression model) were also performed to test the robustness of PFS and showed similar estimates. The PFS benefit with lenvatinib + everolimus was consistent across all subgroups. However, these subgroup analyses should be considered exploratory as the study was not powered to detect differences between the subgroups.

OS was a secondary outcome in the HOPE-205 trial. OS was assessed at one pre-planned and two ad-hoc updated OS analyses. At the date of the first ad-hoc updated OS analysis (December 10, 2014), a median OS of 25.5 months (95% CI, 16.4 to not estimable) for the lenvatinib + everolimus arm and 15.4 months (95% CI, 11.8 to 20.6) for the everolimus arm were observed (stratified HR = 0.51; 95% CI, 0.30 to 0.88; *P* = 0.02). At the date of the latest updated OS analysis (July 31, 2015), a median OS of 25.5 months (95% CI, 16.4 to 32.1) for the lenvatinib + everolimus arm and 15.4 months (95% CI, 11.8 to 20.6) for the everolimus arm (stratified HR = 0.59; 95% CI, 0.36, 0.96; *P* = 0.06) were observed.

Patient-reported outcomes: Not measured

The HOPE-205 trial did not collect patient-reported outcomes.

Safety: Higher toxicity with lenvatinib in combination with everolimus, however, manageable.

pERC discussed that lenvatinib in combination with everolimus increased toxicity compared with everolimus monotherapy. The most common treatment-emergent adverse events (TEAEs) of any grade were in the lenvatinib in combination with everolimus arm: diarrhea (85% with lenvatinib + everolimus and 34% with everolimus) and fatigue or asthenia (59% with lenvatinib + everolimus and 38% with everolimus). The incidence of grade 3 or 4 TEAEs was higher in the lenvatinib + everolimus arm at 71% (36/51), compared with 50% (25/50) in the everolimus arm. This higher incidence was mainly driven by grade 3 TEAEs: diarrhea (20% with lenvatinib + everolimus versus 2% with everolimus), hypertension (14% with lenvatinib + everolimus versus 2% with everolimus), fatigue (14% with lenvatinib + everolimus versus 0% with everolimus), anemia (8% with lenvatinib + everolimus versus 12% with everolimus), hypertriglyceridemia (8% with either lenvatinib + everolimus or everolimus), and vomiting (8% with lenvatinib + everolimus versus 0% with everolimus). Seven (14%) patients receiving lenvatinib + everolimus were reported to have grade 4 TEAEs, as compared with four (8%) patients in the everolimus arm. Grade 3 or worse serious AEs occurred more frequently in patients assigned to lenvatinib + everolimus (23/51; 45%) than in those assigned to everolimus (19/50; 38%).

Overall, 12/51 (24%) patients in the lenvatinib + everolimus arm, and 6/50 (12%) of those in the everolimus arm discontinued study treatment due to adverse events. One patient in the lenvatinib + everolimus arm died due to cerebral hemorrhage that was judged by the investigators to be related to the study drug; and two patients assigned to receive everolimus died due to acute respiratory failure and sepsis (neither of which were judged to be treatment-related).

Limitations: No direct comparative data to standard care options: nivolumab and axitinib.

The submitter provided an ITC to provide estimates of comparative efficacy between lenvatinib in combination with everolimus and other comparators in the treatment of patients with advanced or metastatic, clear-cell RCC following one prior VEGF-targeted therapy. This network of trials in the ITC permitted comparisons of lenvatinib + everolimus with cabozantinib, nivolumab, and everolimus monotherapy. Cabozantinib was not regarded as a relevant comparator at the time of this pCODR review, as it is currently under review with pCODR and not publicly funded in any of the participating jurisdictions. Axitinib was not included in the submitted ITC due to concerns with transitivity (different eligibility criteria). The indirect comparisons were performed using a network meta-analysis with parametric fractional polynomial survival functions which do not rely on the proportional hazard assumption. The pCODR Methods Team assessed the quality of the ITC provided by the submitter according to the recommendations made by the ISPOR Task Force on Indirect Treatment Comparisons. Although the point estimates of effect resulting from the ITC (HR < 1) suggested that lenvatinib + everolimus could be superior to everolimus monotherapy and nivolumab in terms of PFS and OS, these results should be interpreted with caution due to several limitations. pERC agreed with the Methods Team that, given the limitations in the underlying data, overlapping credible intervals (i.e., statistical non-significance), limitations arising from the lack of closed loops in the network, the limited number of studies for each treatment comparison (one study per comparison), and lack of indirect comparisons for safety data and other efficacy outcomes (e.g., ORR, QoL), the comparative effectiveness of lenvatinib in combination with everolimus versus nivolumab remained uncertain. In addition, because the submitted ITC did not include axitinib, no conclusions could be made on the relative efficacy of lenvatinib + everolimus compared with axitinib.

Need and burden of illness: Need for treatment that delays disease progression and improves overall survival.

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2017, there were 6,600 new cases and 1,900 kidney cancer deaths. About 90% of kidney cancers are RCCs; 80% of all RCCs are of clear-cell histology, and 20% are classified as non-clear cell cancers. In localized stages of RCCs survival rates range from 70% to 90%, but drop to 50% to 60% for patients with more extensive tumours. Patients with metastatic disease are rarely cured, with a median OS of 28 to 32 months. The current standard of care for patients with advanced or metastatic, clear-cell RCC who have had one prior VEGF-targeted therapy includes nivolumab, which is the most commonly used therapy, axitinib, or everolimus. Despite current treatment options, long-term survival and cure are still rare for patients with metastatic RCC, particularly

in the second-line setting, with less than 10% of metastatic patients surviving for five years or longer. pERC agreed that there is a need for more effective and less toxic novel therapies, which overcome disease resistance, delay disease progression and improve OS.

Registered clinician input: Lenvatinib in combination with everolimus meets unmet need based on HOPE-205 trial results.
The two registered clinician groups providing input reported that lenvatinib in combination with everolimus would meet a current unmet need in the metastatic RCC space. The clinician groups outlined efficacy results in the HOPE-205 trial, noting that PFS was prolonged with lenvatinib in combination with everolimus compared with everolimus alone (14.6 versus 5.5 months). Improved OS of 10 months for everolimus in combination with lenvatinib compared with everolimus alone and an improved ORR (43% versus 6%) was also mentioned. The clinician groups made note of a consistent safety profile of the combination therapy compared with each agent individually, and indicated that toxicities would be manageable. In addition, one clinician group noted that the ability of the drug combination to target both the receptor tyrosine kinase and the mechanistic target of rapamycin (mTOR) pathway is advantageous. In terms of sequencing, the clinician groups were not certain as to where in the treatment pathway the drug combination fits; one clinician group provided a reference to a figure that outlines treatments in second-line and beyond for metastatic kidney cancer. In the other clinician input, it was suggested that lenvatinib in combination with everolimus would either be given before or after nivolumab. Companion diagnostic testing is not required for the new drug.

PATIENT-BASED VALUES

Values of patients with renal cell carcinoma: delay disease progression, alternative choices
The most commonly reported side effects experienced by patients as a result of previously used therapies in kidney cancer were fatigue and a lack of energy, diarrhea, loss of appetite, and hand-foot syndrome. While the majority of patients stated that these side effects were tolerable, a significant proportion (27%) indicated that the toxicity was difficult to tolerate.

In terms of considerations for new therapies, patients valued long-term stability or reduction of disease, improved quality of life and physical condition, as well as having new, effective second-line treatment alternatives that offer more patient choice within the same line of therapy to overcome drug resistance, control drug resistance mechanisms and choose between side effects. It was also noted that by incorporating more choices for drug treatments, patients and physicians can implement treatment plans that are tailored to the individual and enable the best possible outcomes and QoL for patients.

Patient values on treatment: very effective, tolerable side effects, high quality of life
In regards to lenvatinib in combination with everolimus, 14 patients across Canada reported having experience with this combination of drugs. Three patients surveyed were interviewed in depth about their experiences. These patients gained access to lenvatinib in combination with everolimus through various means, for example, through insurance, clinical trials, and access programs. The majority of patients considered lenvatinib and everolimus to be a very effective therapy against their kidney cancer affording them a high QoL with side effects that were well tolerated. Of the 13 side effects reported by patients who received lenvatinib in combination with everolimus, cough was reported as being most difficult to tolerate followed by hand-foot syndrome, loss of appetite, diarrhea, fatigue/loss of energy, and nosebleeds. Most patients agreed that the benefits of the lenvatinib combination outweighed the experience of the side effects.

KCC indicated that they are able to collect real-world data from medical centres across the country via their affiliated research arm, the Kidney Cancer Research Network of Canada, which is a Web-based national registry.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility and cost-effectiveness analyses
The pCODR Economic Guidance Panel (EGP) assessed one cost-utility analysis (clinical effects measured by quality-adjusted life-years gained) and one cost-effectiveness analysis (clinical effects measured by life-

years gained) of lenvatinib in combination with everolimus compared with everolimus monotherapy for the treatment of patients with advanced or metastatic, clear-cell RCC following one prior VEGF-targeted therapy.

Basis of the economic model: Clinical and economic inputs

The key clinical outcomes considered in the cost-utility analysis were PFS, OS, and utilities.

Costs considered in the analysis included those related to drug and administration costs, disease management, end of life, and AEs.

Drug costs: Treatment cost of lenvatinib in combination with everolimus and comparators

Lenvatinib costs $8.14 per mg or $732.86 per unit (five-day blister card). At the recommended dose of 18 mg once daily (1 mg X 10 mg, 2 mg X 4 mg capsules), lenvatinib costs $146.57 per day. At the recommended dose of 5 mg once daily (one 5 mg tablet), everolimus costs: $202.65 per day. Lenvatinib in combination with everolimus cost $8,896.00 per 28-day drug cycle.

Everolimus monotherapy: At the recommended dose of 10 mg/day (two 5 mg tablets), everolimus costs: $5,704.00 per 28-day cycle.

Axitinib costs $97.13 per 5 mg tablet. At the recommended dose of 5 mg twice daily, axitinib costs $194.26 per day and $5,469.00 per 28-day cycle.

Nivolumab costs $1,955.56 per 100 mg vial. At the recommended dose of 3 mg/kg every two weeks, the cost of nivolumab is $5,866.68 per day and $11,842.00 per 28-day cycle.

Cost-effectiveness estimates: clinical effectiveness estimates cannot be used to inform credible incremental cost-effectiveness ratios

The submitter provided an economic evaluation to assess the cost-effectiveness of lenvatinib in combination with everolimus compared with everolimus monotherapy, axitinib, and nivolumab in patients with clear-cell advanced or metastatic RCC. pERC noted that the EGP's reanalyses of cost-effectiveness presented incremental cost-effectiveness ratios (ICERs) as lower bounds with no upper bounds, given the uncertainty around the clinical comparative efficacy of treatments. pERC also noted that the submitted base-case ICERs were lower than the EGP's lower bound ICER estimates. This was primarily due to two factors:

- A shorter time horizon (10 years instead of 20 years): the time horizon was shortened to address uncertainty in survival estimates based on extrapolation of short-term trial data and to maintain consistency with other pCODR reviews. A 10-year time horizon for survival was supported by the CGP.
- Shorter duration of treatment effect (60 months instead of 240 months): the EGP shortened the duration of treatment, as it is unlikely that any benefit from treatment would extend indefinitely once a patient progresses on that treatment. Given the reliance on ITC data, the EGP elected to set all treatment effects to the equivalent of everolimus at 60 months (unless the treatment effect was originally lower than that of everolimus, in which case, the treatment effect remained unchanged).

pERC noted several limitations in the submitted analyses, particularly the uncertainty in the clinical comparative efficacy data. The submitter provided an ITC to provide relative treatment effect estimates between comparators in the absence of head-to-head data. The indirect comparison suggested that there was no statistically significant difference in PFS or OS between lenvatinib in combination with everolimus and nivolumab and everolimus monotherapy, as seen by the 95% credible intervals crossing 1.0. However, the economic model suggested a benefit of lenvatinib in combination with everolimus versus all comparators, including axitinib (which assumed a similar efficacy as everolimus). As the EGP was unable to quantify this uncertainty in the effectiveness data, the EGP elected to place no upper bound on its best-case estimate. pERC noted that one reason the EGP was unable to explore the uncertainty in the effectiveness data was that the submitter had fitted fractional polynomials instead of using HRs to estimate treatment effects as the proportional hazard assumption did not hold. Fitting curves for fractional polynomials relies on an average fit across all interventions, instead of choosing different curves for each treatment. In the case of OS, the best fitting curve (according to fit statistics) visually aligned better with lenvatinib + everolimus than with nivolumab. The result is that OS predictions may

have been underestimated for nivolumab. In addition, pERC noted that in the probabilistic sensitivity analysis, the submitter assumed a 20% distribution around efficacy inputs. pERC noted the EGP's opinion that this 20% is an arbitrary assumption of uncertainty and does not reflect the variability in the results due to parameter uncertainty. Further, utilities were not collected in the HOPE 205 trial, but utilities from the AXIS trial were used and generalized to all treatments included in the ITC. Given that the utilities were already collected in the population for axitinib, applying disutilities to this population may be double counting. Finally, subsequent treatments were not included in the submitted model; however, all patients included in the ITC received a subsequent line of therapy after discontinuing the treatment under study. Hence, estimates of survival from these studies would include any potential benefit received from these treatments, without accounting for the cost of these subsequent treatments.

pERC agreed that the estimates of incremental effectiveness are largely based on a key clinical assumption that the efficacy results observed in the HOPE-205 trial and the submitted ITC translate into real and meaningful improvements in PFS and OS in the lenvatinib combination compared with other currently available therapies. Given the Committee's lack of confidence in the treatment effect estimates for lenvatinib in combination with everolimus due to the limitations in the evidence from the available phase II clinical trial and the ITC analysis, and the inability of the economic model to account for the resulting uncertainty in the parameter estimates, pERC agreed that the clinical effectiveness estimates could not be used to inform credible ICER estimates. Therefore, pERC could not draw a conclusion on the cost-effectiveness and could not determine the ICER of lenvatinib in combination with everolimus compared with everolimus monotherapy, nivolumab, or axitinib for the treatment of patients with advanced or metastatic, clear-cell RCC following one prior VEGF-targeted therapy.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact underestimated
pERC considered the feasibility of implementing a reimbursement recommendation for the lenvatinib combination for the treatment of patients with advanced or metastatic, clear-cell RCC following one prior VEGF-targeted therapy. pERC discussed PAG's request for clarity on sequencing of treatments, on whether treatment with single agent lenvatinib or single agent everolimus is appropriate in patients with intolerance to lenvatinib in combination with everolimus, and whether the HOPE-205 trials results could be generalized to certain patient subgroups not included in the HOPE-205 trial. pERC also considered that lenvatinib in combination with everolimus is a high-cost regimen and that the submitted Canada-wide budget impact was likely underestimated. pERC noted that according to the submitted base case introducing lenvatinib in combination with everolimus to the market resulted in savings over three years. pERC discussed that possible reasons for the savings could be the treatment duration and acquisition cost of nivolumab. pERC noted that the submitted total three-year budget impact of lenvatinib in combination with everolimus increases by about 4.5% (rendering the treatment-funded scenario more expensive and eliminating any savings) if the treatment duration of nivolumab is decreased from seven to 5.5 months, and decreases by about 29% (rendering the treatment-funded scenario cheaper and increasing savings) if the treatment duration of nivolumab is increased from seven to 16 months. Further, increasing the proportion of patients eligible to receive lenvatinib in combination with everolimus through publicly funded drug plans from 49% to 95%, decreases the total three-year budget impact of lenvatinib in combination with everolimus by about 0.5% (rendering the treatment-funded scenario cheaper and increasing savings). pERC noted that a key limitation of the budget impact analysis is the inclusion of patients younger than 18 in the population estimates, as the funding aligns with the patient population in the HOPE 205 trial, which limited eligibility to patients at least 18 years of age or older. Overall, the Committee concluded that the budget impact is likely underestimated.

DRUG AND CONDITION INFORMATION

Drug Information	• Lenvatinib is a multiple receptor tyrosine kinase inhibitor. • Oral lenvatinib is administered at a dose of 18 mg once daily (one 10 mg capsule and two 4 mg capsules). Oral everolimus should be co-administered at a dose of 5 mg once daily (one 5 mg tablet).
Cancer Treated	• Advanced or metastatic, clear-cell renal cell carcinoma.
Burden of Illness	• In 2017, there were 6,600 new cases and 1,900 kidney cancer deaths. About 90% of kidney cancers are renal cell cancers (RCCs); 80% of all RCCs are of clear-cell histology and 20% are classified as non-clear cell cancers. Patients with metastatic disease are rarely cured with a median overall survival of 28 to 32 months.
Current Standard Treatment	• Nivolumab, axitinib, and everolimus
Limitations of Current Therapy	• Despite current treatment options, long-term survival and cure are still rare for patients with metastatic RCC, particularly in the second-line setting, with less than 10% of metastatic patients surviving for five years or longer

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:

pERC Membership During Deliberation of the Initial Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Economist
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. Dominika Wranik, Economist

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

- Dr. Anil Abraham Joy, and Dr. Winson Cheung, who were not present for the meeting.
- Daryl Bell, who did not vote due to his role as a patient member alternate.
- Dr. Christian Kollmannsberger, who was excluded from voting due to a conflict of interest.

pERC Membership During Deliberation of the Final Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist

Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Economist
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Economist

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

- Daryl Bell, who did not vote due to his role as a patient member alternate
- Dr. Christian Kollmannsberger and Dr. Henry Conter, who were excluded from voting due to a conflict of interest.

Avoidance of conflicts of interest

All members of pERC 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 lenvatinib (Lenvima) for renal cell carcinoma, through their declarations, two members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, two of these members were excluded from voting.

Information sources used

pERC 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 its 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*. 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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