pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The 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 cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

Providing Feedback on this Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Trametinib (Mekinist)

Submitted Funding Request:
For use as a monotherapy for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Submitted By:
GlaxoSmithKline

Manufactured By:
GlaxoSmithKline

NOC Date:
July 18, 2013

Submission Date:
May 6, 2013

Initial Recommendation Issued:
October 3, 2013

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) recommends funding trametinib (Mekinist) in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, conditional on the cost-effectiveness of trametinib being improved to an acceptable level. Funding should be for untreated patients or patients previously treated with chemotherapy with ECOG performance status 0 or 1. If brain metastases are present, they should be stable. The Committee made this recommendation because it was satisfied that there is a net clinical benefit of trametinib compared with dacarbazine. However, at the submitted price and the Economic Guidance Panel's best estimates of the incremental cost-effectiveness ratio, trametinib could not be considered cost-effective compared with dacarbazine. In the absence of a direct comparison with vemurafenib, the clinical benefit and the uncertainty in the economic analyses was too great for the Committee to determine the net clinical benefit or cost-effectiveness compared with vemurafenib.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC was satisfied that there is a net clinical benefit of trametinib in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of trametinib to an acceptable level. **Confirming Cost-Effectiveness of Trametinib** Provinces should be aware that the cost-effectiveness estimates of trametinib compared with vemurafenib assumed that the price of vemurafenib in all jurisdictions is the same as the list price. Therefore, any changes in the price of vemurafenib could considerably change the cost-effectiveness of trametinib compared with vemurafenib.

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Implementation of Trametinib and BRAF Mutation Testing
Because use of trametinib requires patients to have BRAF V600 mutation positive melanoma, funding for trametinib should not be made available unless funding for diagnostic testing of BRAF V600 mutations is also available

Guideline Needed to Inform Treatment Sequencing in Metastatic Melanoma
pERC noted that a number of new agents have recently become available to treat metastatic melanoma but there is currently no evidence on the sequential use of these treatments. pERC recognized that the optimal sequencing of these treatments is still unknown and pERC was unable to make an informed recommendation on the use of trametinib in patients who have progressed while receiving ipilimumab or a BRAF inhibitor. However, pERC recognized that provinces will need to address this issue upon implementation of funding and noted that the development and implementation of an evidence-based guideline would be of value.

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SUMMARY OF pERC DELIBERATIONS

pERC noted that metastatic melanoma affects a small patient population but the incidence is increasing. pERC also recognized that, until recently, there have been very few effective treatment options for metastatic melanoma and there is a need for new and effective therapies in this setting. One randomized controlled trial comparing trametinib, a MEK inhibitor, with dacarbazine in both untreated patients and patients treated with prior chemotherapy (METRIC, Flaherty 2012) was included in the pCODR systematic review. pERC noted that at the time the trial was designed, dacarbazine was an appropriate comparator. However, vemurafenib, a BRAF inhibitor, which has recently become available is now standard of care in patients who are BRAF mutation positive.

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated upon the results of the METRIC study and concluded that there is a net clinical benefit of trametinib compared with dacarbazine in both untreated patients and patients previously treated with chemotherapy. pERC noted that there was a significant improvement in overall survival favouring trametinib. pERC also discussed the quality of life results from the METRIC study and noted that quality of life did not deteriorate with trametinib, although interpretation of these data was challenging. pERC discussed the toxicity profile of trametinib based on adverse events observed in the METRIC study and considered that toxicities were manageable compared with dacarbazine. pERC noted that in the absence of a head-to-head trial, the relative efficacy and safety of trametinib compared with vemurafenib was uncertain. pERC discussed the results of an indirect comparison of trametinib and vemurafenib conducted by the manufacturer but noted that there are limitations to indirect and cross-trial comparisons. However, pERC noted that the pCODR Clinical Guidance Panel considered that trametinib may provide another treatment option for patients who do not tolerate toxicities associated with BRAF inhibitors such as phototoxicity and arthralgia.

pERC reviewed input from one patient advocacy group and determined that trametinib aligns with patient values. Patients indicated that they valued extending life and improvements in quality of life. Patients also reported that, even with the newly available treatments for metastatic melanoma, therapies can be difficult to tolerate and having additional treatment options available would be valued. pERC considered this input in the context of the METRIC study, which demonstrated that trametinib extends life and has manageable toxicities compared with dacarbazine and concluded that trametinib aligns with patient values.

pERC deliberated upon the cost-effectiveness of trametinib, which was strongly influenced by the price of trametinib. pERC considered that using either the manufacturer's or the pCODR Economic Guidance Panel's estimates, trametinib was not cost-effective at the submitted price compared with dacarbazine. pERC noted that the manufacturer's economic analysis was based only on untreated patients but that additional analyses conducted by pCODR's Economic Guidance Panel suggested that the cost-effectiveness of trametinib in patients previously treated with chemotherapy would likely be similar to cost-effectiveness in untreated patients. pERC also discussed the cost-effectiveness of trametinib compared with vemurafenib. However, pERC noted that there was considerable uncertainty in the incremental cost effectiveness ratios based on the indirect comparison of trametinib with vemurafenib. In addition, pERC noted that the economic analysis was based on the list price of vemurafenib but acknowledged that the effective price of vemurafenib is unknown and may vary across jurisdictions. Therefore, pERC considered that there was too much uncertainty to determine the relative cost-effectiveness of trametinib compared with vemurafenib.

pERC discussed the feasibility of implementing a funding recommendation for trametinib. It was noted that because the clinical effect of trametinib is limited to patients with the BRAF V600 mutation, diagnostic testing is essential and funding for trametinib should only be made available if funding for the test is also available. Input from pCODR's Provincial Advisory group indicated that BRAF testing is now available in some jurisdictions so some patients will already have access to testing. pERC also discussed

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that a number of new treatments for metastatic melanoma have recently become available. pERC noted that, currently, there is no information to inform a recommendation on the use of trametinib in patients who have progressed while receiving ipilimumab or a BRAF inhibitor, but that development of an evidence-based guideline to inform treatment algorithms and the appropriate sequencing of drugs in metastatic melanoma would be useful.

EVIDENCE IN BRIEF

pERC deliberated upon a pCODR systematic review, other literature in the Clinical Guidance Report providing 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 (Melanoma Network of Canada) and input from pCODR's Provincial Advisory Group.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the efficacy and safety of trametinib compared with standard treatment, placebo, or best supportive care in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Studies included: one RCT in untreated and previously treated patients

The pCODR systematic review included one open-label, randomized controlled trial (N=322), the METRIC study (Flaherty 2012) which evaluated the efficacy and safety of trametinib (2 mg orally once daily), compared with dacarbazine (1000mg/m^2 every 3 weeks) or paclitaxel (175 mg/m^2 every 3 weeks). Patients in the chemotherapy group were allowed to cross over to receive trametinib after disease progression had been confirmed by an independent review. At the time of the first data cut-off (Oct 2011), 47% of patients randomized to chemotherapy had crossed over to receive trametinib, which may have confounded overall survival results from the study.

The pCODR review also provided contextual information on:

- relevant comparators including a critical appraisal of an indirect comparison of trametinib (METRIC, Flaherty 2012) and vemurafenib (BRIM-3, Chapman 2011)
- BRAF mutation testing in metastatic melanoma

Patient populations: untreated and previously treated, BRAF V600E and V600K mutation positive, stable brain metastases

The METRIC study included patients with ECOG status of 0 and 1 (64% versus 36%, respectively) and who were either BRAF V600E or BRAF V600K mutation positive (87% and 13%, respectively). pERC noted that only a small proportion of patients with the V600K mutation were included in the trial and as a result, subgroup analyses may not have sufficient power to demonstrate a potential benefit in this group. However, pERC considered that because patients with both BRAF V600E and V600K mutations were included in the trial, funding should not be restricted by the specific V600 mutation sequence. pERC considered that because the clinical effect of trametinib is limited to patients with a BRAF V600 mutation, diagnostic testing for BRAF V600 mutation status is essential and funding for trametinib should only be made available if funding for the test is also available.

Patients were generally well balanced in demographics between the two arms. Patients in both trametinib and dacarbazine arms could have had previous chemotherapy (33% and 35%, respectively). Patients could be included in the METRIC study if brain metastases were stable, however, the definition of stable was not provided. Approximately 4% of the trametinib group had a history of brain metastasis compared to 2% in the chemotherapy group.

Key efficacy results: improvement in overall survival and progression-free survival

Key outcomes deliberated on by pERC included progression free survival (PFS) in the primary efficacy population, the primary endpoint, while secondary efficacy outcomes included overall survival and PFS in

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the intention-to-treat (ITT) population and in subgroups of the primary efficacy population. Improvements in both overall survival and progression-free survival were observed, therefore, pERC concluded that there is a net clinical benefit of trametinib compared with dacarbazine in both untreated patients and patients previously treated with chemotherapy.

Median PFS in the primary efficacy population was 4.8 and 1.5 months in the trametinib and chemotherapy group, respectively (HR 0.44, 95% CI: 0.31 to 0.64 p<0.0001). Similar results were observed for both untreated patients (HR=0.44, 95% CI, 0.28 to 0.69) and previously treated patients (HR=0.52, 95% CI, 0.29 to 0.93). A significant improvement in PFS was also observed for patients with BRAF V600E mutation but not with V600K mutations. pERC discussed these results but noted that the small number of patients with V600K mutation may contribute to the lack of statistical significance in the subgroup analysis.

For the secondary outcome, median overall survival was longer in the trametinib arm at the October 2011 analysis (HR=0.54, 95%CI: 0.32 to 0.92, P=0.01) but not the May 2013 analysis (HR=0.78, 95%CI: 0.57 to 1.06, P=0.0912). However, pERC noted that overall survival may have been confounded by crossover as patients in the METRIC study were permitted to cross-over from dacarbazine treatment to trametinib treatment upon disease progression.

Quality of life: no deterioration in quality of life with trametinib

pERC discussed quality of life outcomes from the METRIC study and noted that it appeared quality of life did not deteriorate in patients receiving trametinib. However, given the lack of statistical assessment of these data, the interpretation of results was challenging

Safety: acceptable and manageable toxicity profile compared with dacarbazine

pERC discussed the toxicity profile of trametinib demonstrated in the METRIC study. The proportion of patients with serious adverse events was similar between trametinib and dacarbazine. In the trametinib group, the most common adverse events were rash, diarrhea, peripheral edema, fatigue, hypertension and dermatitis acneiform. A decreased ejection fraction occurred in 7% patients and serious grade 3 cardiac events occurred in 0.01% patients. Ocular events occurred in 9% patients. pERC noted that the cardiac and ocular events are generally reversible upon discontinuation of treatment. It was also noted that no second primary malignancies were observed, which was as expected based on the mechanism of action of trametinib. Therefore, pERC considered that toxicities appeared tolerable and manageable compared with dacarbazine.

Comparator information: uncertainty of efficacy and safety compared with vemurafenib

pERC noted that according to the Provincial Advisory Group's input and the pCODR Clinical Guidance Panel, the current standard treatment for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma is vemurafenib. The METRIC study compared trametinib with dacarbazine. Therefore, pERC considered the results and critical appraisal of an indirect comparison of trametinib (METRIC, Flaherty 2012) with vemurafenib (BRIM-3, Chapman 2011), which had been conducted by the manufacturer. However, pERC noted that conclusions drawn from such indirect comparisons are not as robust as those from direct, head-to-head trial data and, therefore, the findings should be interpreted with caution. pERC noted that factors such as the length of available follow-up data had a significant impact on the results of the indirect comparison. pERC discussed that in the absence of a head-to-head trial, the relative efficacy and safety of trametinib compared with vemurafenib remains uncertain. However, pERC noted that the patient advocacy group input indicated that not all patients can tolerate adverse events associated with new melanoma treatments. Therefore, trametinib may provide another treatment option for patients who do not tolerate BRAF inhibitors due to toxicities such as phototoxicity and arthralgia

Need: effective treatment options for patients who cannot tolerate BRAF inhibitors

pERC discussed that until recently, there have been no effective therapies to treat metastatic melanoma. It was noted that there is no evidence that dacarbazine improves overall survival and has associated side effects that patients frequently find difficult to tolerate. pERC noted that although vemurafenib has recently become the standard treatment for patients who are BRAF V600 mutation positive, there is still a need for new effective treatments that would allow patients a choice of therapies. Patient advocacy group input indicates that patients experience serious and severe side effects with currently available

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therapies and seek alternative treatment options. pERC noted that trametinib has an acceptable toxicity profile. Therefore, it may be an effective alternative and meet an important need for patients intolerant to a BRAF inhibitor. pERC also noted that patients with metastatic melanoma are often young and while this cancer may affect a small patient population, the incidence is increasing.

PATIENT-BASED VALUES

Values of patients with metastatic melanoma: extending life and improving quality of life

pERC discussed input on trametinib provided by one patient advocacy group. Input indicated that without treatment, patients with metastatic melanoma face the certainty of disease progression or death. Worsening of symptoms as disease progresses may include increasing shortness of breath, severe pain, fatigue, memory loss, loss of coordination, cognitive impairment from brain metastases or radiation, loss of sight, lymphedema and weight loss. Therefore, from a patient perspective, the primary concerns of patients with melanoma include increasing life expectancy and controlling disease. From a patient perspective, while there are therapies approved for metastatic patients that have a positive impact on overall survival rates, these drugs do not work effectively for all advanced stage patients. pERC considered this input in the context of the METRIC study, which demonstrated trametinib improves progression-free survival and overall survival compared with dacarbazine and concluded that trametinib aligns with these patient values. Patients also reported that the newer treatment options for metastatic melanoma have made a substantial positive impact on their quality of life. The majority of patients ranked the importance of quality of life while on treatment as either important or very important. pERC considered that the interpretation of quality of life outcomes from the METRIC study was challenging, but it appeared that patients receiving trametinib did not experience a decline in quality of life. Therefore, pERC agreed that trametinib aligned with these patient values.

Patient values on treatment: side effects tolerable, choice of treatment options

Patient advocacy group input reported on patients' experiences with the side effects of treatments for metastatic melanoma. Depending upon the site of metastases and type of treatment, many patients suffer from adverse events such as headaches, neuropathy, bone fractures, blindness, hair loss, depression, anxiety, memory loss, decreased mobility, colitis, and disfiguring surgeries. Many patients have had extensive surgery to remove lymph nodes and/or tumours, which has caused decreased mobility, loss of functioning or capacity of certain organs, scarring and negative body image issues.

In general, patient advocacy group input indicates that patients experience serious and severe side effects with currently available therapies and seek alternative treatment options. The majority of patients are willing to accept side effects and serious risks associated with a future new drug if the side effects can be effectively managed. Additionally, patients indicated that they would be willing to tolerate potential side effects if they knew the results would extend their lives, even if the benefits of the treatment were only short-term. Patients also reported that, even with the newly available treatments for metastatic melanoma, therapies can be difficult to tolerate and having additional treatment options available would be valued. pERC considered this input in the context of the METRIC study, which demonstrated that the toxicity profile of trametinib was tolerable. Therefore, trametinib aligns with these patient values. pERC also noted that trametinib is an oral treatment and the number of tablets required each day is less for trametinib than for vemurafenib (1 versus 8 tablets), which patients would prefer.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost utility

The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness analysis of trametinib monotherapy compared to dacarbazine in the first-line treatment of patients with BRAF mutation positive unresectable or metastatic melanoma based on the subset of untreated patients in the METRIC study. An economic analysis comparing trametinib with vemurafenib based on an indirect comparison was also assessed. The manufacturer did not provide any analyses of trametinib in previously treated patients.

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Basis of the economic model: clinical and economic inputs

Costs included in the analysis were drug costs, costs associated with treatment of adverse events, diagnostic testing costs, and pre and post-progression background treatment costs.

Key clinical effects included in the analysis versus dacarbazine were overall survival and progression free survival, based on data from the METRIC study. The analysis versus vemurafenib was based on the indirect comparison of data derived from the METRIC and BRIM 3 trials.

Drug costs: uncertainty in pricing

At the list price, trametinib costs $72.50 and $290.00 per 0.5 and 2 mg tablets, respectively. At the recommended dose of 2 mg once daily, the cost of trametinib is $290 per day. The average cost per 28-day course is $8,120.

At the list price, vemurafenib costs $46.50 per 240 mg tablet. At the recommended dose of 960 mg twice daily (8 tablets per day), the cost of vemurafenib is $372 per day. The average cost per 28-day course is $10,425. In the main analysis, the manufacturer assumed that in all jurisdictions, the price of vemurafenib is the same as the list price. pERC recognized that the effective price of vemurafenib may however vary across jurisdictions and may be lower than the list price used in the analysis. pERC noted that this created substantial uncertainty in the cost-effectiveness of trametinib relative to vemurafenib.

Cost-effectiveness estimates: not cost-effective compared with dacarbazine, uncertainty in cost-effectiveness compared with vemurafenib

pERC deliberated upon the cost-effectiveness of trametinib and discussed the pCODR Economic Guidance Panel's critique of the manufacturer's economic analysis.

pERC noted that the economic analysis was strongly influenced by the price of trametinib and other factors such as the time horizon and estimates of progression-free survival and overall survival. pERC noted that the manufacturer's estimates of cost-effectiveness compared with dacarbazine were similar to the pCODR Economic Guidance Panel's estimates. However, at the range of incremental cost-effectiveness ratios reported and at the submitted price, pERC concluded that trametinib was not cost-effective compared with dacarbazine.
pERC noted that the manufacturer's economic analysis was based only on untreated patients but that additional analyses conducted by pCODR's Economic Guidance Panel suggested that the cost-effectiveness of trametinib in patients previously treated with chemotherapy would likely be similar to it's cost-effectiveness in untreated patients.

pERC also discussed the cost-effectiveness of trametinib compared with vemurafenib. pERC noted that there was considerable uncertainty in the incremental cost effectiveness ratios based on the indirect comparison of trametinib with vemurafenib. In particular, pERC noted that there was a very wide range of possible incremental cost-effectiveness ratios and considerable uncertainty where in the range the true cost-effectiveness estimate lies given the limitations of relying on indirect comparisons. In addition, pERC noted that the economic analysis was based on the list price of vemurafenib but that the effective price of vemurafenib is unknown and may vary across jurisdictions. Therefore, pERC considered that there was too much uncertainty to determine the relative cost-effectiveness of trametinib compared with vemurafenib.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: BRAF mutation testing and treatment sequencing

pERC discussed the feasibility of implementing a funding recommendation for trametinib. It was noted that because the clinical effect of trametinib is limited to patients with a BRAF V600 mutation, diagnostic testing is essential and funding for trametinib should only be made available if funding for the test is also available. Input from pCODR's Provincial Advisory group indicated that BRAF testing is now available in some jurisdictions, so many patients will already have access to testing.

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pERC also discussed that a number of new treatments for metastatic melanoma have recently become available. pERC noted that, currently, there is no information to inform a recommendation on the use of trametinib in patients who have progressed while receiving ipilimumab or a BRAF inhibitor, but that development of an evidence-based guideline to inform a treatment algorithm and the appropriate sequencing of drugs in metastatic melanoma would be useful.

DRUG AND CONDITION INFORMATION

Drug Information	• MEK inhibitor • Available as 0.5 mg and 2 mg tablets • Recommended dose of 2 mg once daily, administered orally
Cancer Treated	• Unresectable or metastatic melanoma with a BRAF V600 mutation
Burden of Illness	• 5,500 new cases of primary melanoma are expected in 2011 and approximately 950 patients will die from melanoma. • Unresectable Stage III and IV melanoma is an incurable malignancy with approximately 6% of patients surviving 5 years, and 75% percent of patients dying within one year of diagnosis
Current Standard Treatment	• Vemurafenib is currently a standard first line treatment for advanced, unresectable melanoma in patients with a BRAF V600 mutation. • Until recently, dacarbazine was standard first-line treatment although it does not have an overall survival benefit and has serious toxicities
Limitations of Current Therapy	• Newer treatments may not be tolerated by all patients, therefore, there is a need for effective alternative therapies

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist;
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Lister, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Jo Nanson, Dr. Chaim Bell, Dr. Sunil Desai, Dr. Tallal Younis and Mario de Lemos who were not present for the meeting

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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 review of trametinib (Mekinist) for metastatic melanoma, through their declarations, eight members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting.

Information sources used

The pCODR Expert Review Committee 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 their 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*.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers 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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