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:
Brentuximab Vedotin (Adcetris)

Submitted Funding Request:
For second-line treatment of sALCL patients - i.e. after failure of at least one prior multi-agent chemotherapy regimen

Submitted By:
Seattle Genetics, Inc.

Manufactured By:
Seattle Genetics, Inc.

NOC Date:
February 1, 2013

Submission Date:
March 15, 2013

Initial Recommendation Issued:
October 3, 2013

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) recommends funding brentuximab vedotin (Adcetris) monotherapy in patients with systemic anaplastic large cell lymphoma (sALCL) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for patients who have failed at least one prior multi-agent chemotherapy regimen and who have an ECOG performance status of 0 or 1. pERC made this recommendation because the Committee considered that there is a net clinical benefit of brentuximab based on improvements in progression-free survival and a meaningful proportion of patients with a durable complete response. pERC also considered that a randomized controlled trial was not thought to be feasible, the clinical course of sALCL is very aggressive, the patient population to whom this recommendation applies is small, and there are no other effective, non-toxic therapeutic options. However, pERC acknowledged that because of the non-randomized, non-comparative phase two study design, there was considerable uncertainty around the magnitude of the benefit and, therefore, in the cost-effectiveness of brentuximab. This led to a wide range of incremental cost-effectiveness estimates, all of which pERC considered unacceptable. Therefore, brentuximab could not be considered cost-effective at the submitted price.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC was satisfied that there is a net clinical benefit of brentuximab vedotin in patients with a systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of brentuximab to an acceptable level. pERC noted that the cost per cycle of brentuximab was extremely high and that drug price was the key driver of the incremental cost-effectiveness

estimates. Therefore, to offset the considerable uncertainty in the clinical effect estimates, pERC concluded that a substantial reduction in drug price would likely be required in order to improve cost-effectiveness.

Collecting Prospective Evidence to Reduce Uncertainty in Cost-Effectiveness and to Determine Impact of Subsequent SCT

Given the considerable uncertainty in the magnitude of clinical benefit of brentuximab vedotin in patients with systemic anaplastic large cell lymphoma (sALCL), pERC concluded that any additional prospective evidence that could be collected to decrease the uncertainty in the incremental effect would be of benefit in understanding the true cost-effectiveness of brentuximab. In addition, pERC noted that there was considerable uncertainty in the magnitude of clinical benefit in study SG035-0004 because outcomes may have been confounded by subsequent stem cell transplant (SCT). Therefore, prospective data collection related to the impact of subsequent SCT on survival would help further define the magnitude of clinical benefit of brentuximab in this setting. For example, pERC noted that information on the proportion of:

- patients who receive brentuximab alone and acheive long –term remission,
- patients who receive subsequent SCTs and
- long-term survivors following SCT, would be of interest.

These data could better inform the estimates of clinical benefit and cost-effectiveness of brentuximab.

SUMMARY OF pERC DELIBERATIONS

pERC discussed that systemic anaplastic large cell lymphoma (sALCL) is an uncommon malignancy and that the number of patients with sALCL is relatively small. pERC noted that standard treatments for patients with sALCL can include chemotherapy or radiation but observed that the chemotherapy regimens used in this setting are toxic and their effectiveness is limited. pERC agreed with the pCODR Clinical Guidance Panel that sALCL has a very aggressive clinical course and there is a need for effective treatment options given the limited efficacy and the toxicity of currently available palliative options.

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

One non-randomized study was included in the pCODR systematic review, Study SG035-0004 (Pro et al 2012), which evaluated brentuximab in 58 patients with sALCL who had at least one prior chemotherapy. pERC reviewed the trial population of Study SG035-0004 and noted that some patients in the trial could have been eligible for stem cell transplant (SCT). Therefore, pERC considered that the trial population may have had a better prognosis than patients who would likely be treated with brentuximab in clinical practice. This patient population selected for this trial may have biased the results of the study in favour of brentuximab. pERC deliberated upon the results of Study SG035-0004 and concluded that there is a net clinical benefit of treatment with brentuximab. pERC noted that a substantial proportion of patients obtained complete responses that were durable with brentuximab and that these responses were higher than historical responses observed with other treatments used to treat sALCL. pERC also noted that the length of progression-free survival of patients receiving brentuximab was longer than had been reported for previous treatments for the most recent prior treatment. pERC considered that, in a population who has been previously treated, it was uncommon for progression-free survival to be longer than that observed for previous lines of chemotherapy. In addition, a substantial proportion of patients who received brentuximab were still alive one-year after starting treatment. pERC acknowledged that because of the non-randomized, non-comparative phase two study design, there was considerable uncertainty around the magnitude of the benefit. However, pERC noted that as a result of this trial, equipoise no longer exists and, therefore, it would no longer be feasible to conduct an RCT in this setting. pERC discussed that there was additional uncertainty in the magnitude of benefit due to confounding from subsequent SCT in some patients, which may have resulted in improved outcomes for these patients. Therefore, pERC concluded that prospective data collection to provide additional information on the magnitude of clinical benefit and the impact of subsequent SCT in this setting would be useful.

pERC also discussed the safety of brentuximab in sALCL based on the toxicity profile observed in Study SG035-0004 and concluded that the toxicity of brentuximab was manageable. pERC noted that the most common adverse event was peripheral neuropathy but that the neuropathy was reversible in most patients after discontinuation of brentuximab. pERC noted that no cases of PML were identified in patients who have received brentuximab for sALCL, despite reports in patients with Hodgkin lymphoma. However, pERC noted that only a small number of patients with sALCL have received brentuximab and PML could still be a concern with greater exposure.

pERC discussed input from one patient advocacy group and concluded that brentuximab aligned with patient values. pERC noted that patients with sALCL are willing to try new treatments and have a high tolerance for risk given the high relapse rates of disease. pERC considered that brentuximab would provide patients with an effective treatment option in a setting where there are no effective, non-toxic therapies and that the side effects associated with brentuximab are tolerable.

pERC deliberated on the cost-effectiveness of brentuximab compared with chemotherapy and radiotherapy in patients with sALCL. It was noted that due to the limitations of relying on non-comparative, non-randomized evidence from Study SG035-0004, there was substantial uncertainty in the magnitude of the net clinical benefit associated with brentuximab. In addition, there was substantial uncertainty surrounding the proportion of patients who would receive subsequent stem cell therapy and

its impact on the cost-effectiveness of brentuximab. This made it challenging to estimate the incremental clinical effect of treatment with brentuximab. This considerable uncertainty in the magnitude of net clinical benefit of brentuximab led to a wide range of incremental cost-effectiveness estimates, all of which pERC considered unacceptable. Therefore, brentuximab could not be considered cost-effective at the submitted price

pERC noted that the price of brentuximab was a key driver of cost-effectiveness and that the cost per 28-day cycle of brentuximab was $16,262.40. pERC considered this absolute cost to be extremely high relative to other new high cost cancer drug treatments and that it is above and beyond typical costs. The Committee noted that in order to improve the cost-effectiveness of brentuximab and offset the considerable uncertainty in the incremental effect, a substantial reduction in drug price would likely be required. pERC also considered that additional prospective evidence regarding the magnitude of the clinical benefit of brentuximab, which could inform the understanding of the true cost-effectiveness of brentuximab should be collected.

pERC discussed the feasibility of implementing a funding recommendation for brentuximab in sALCL. pERC noted that due to the small number of patients with sALCL, vial sharing would be unlikely and therefore, drug wastage may be an issue with brentuximab.

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 (Lymphoma Foundation of Canada) and input from pCODR's Provincial Advisory Group.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the safety and efficacy of brentuximab vedotin monotherapy compared to appropriate comparators, in patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.

Studies included: one single-arm study

The pCODR systematic review included one single-arm phase II clinical trial (N=58), the SG035-0004 study (Pro 2012), which assessed the safety and efficacy of brentuximab 1.8 mg/kg, once every 3 weeks for up to 16 cycles or until disease progression or unacceptable toxicity.

No randomized trials were identified that met the eligibility criteria of this systematic review. pERC noted that sALCL is a relatively uncommon malignancy and that the number of patients with sALCL who fail chemotherapy is small. pERC discussed the feasibility of conducting a randomized controlled trial in this population and noted that while it may have been possible at the time the SG035-0004 study was designed, equipoise no longer exists for brentuximab in sALCL. Therefore, pERC considered that it is no longer feasible to obtain information on brentuximab in this setting from a randomized controlled trial.

Patient populations: relapsed after or refractory to chemotherapy

Among patients in the SG035-0004 study, 50% had relapsed after and 50% were refractory to their most recently received therapy. The median number of prior chemotherapy regimens was two (range, 1 to 6). Approximately 45% of patients had prior radiation therapy and 26% had prior ASCT. The patients included in the trial had a median age of 52 years (range, 14 to 76 years) and an ECOG performance status of 0 or 1.

Patients who had previous allogeneic stem cell transplantation were excluded from the study. However, approximately 22% patients received a stem cell transplant following treatment with brentuximab, which may have confounded the survival benefit observed with brentuximab. pERC considered the trial population of Study SG035-0004 and noted that some patients in the trial could have been eligible for stem cell transplant (SCT). Therefore, pERC considered that the trial population may have had a better

prognosis than patients who would likely be treated with brentuximab in clinical practice, which may bias study results in favour of brentuximab.

Key efficacy results: improved PFS, meaningful and durable response rate
Key efficacy outcomes deliberated upon by pERC included objective response rate, the primary outcome of the SG035-0004 study, complete response, duration of response, progression-free survival and overall survival. Objective response rate, as assessed by an independent review committee, was 86% (95% confidence interval [CI], 74.6% to 93.9%) while complete response was 57% (95% CI, 43.2% to 69.8%) in the original analysis. pERC discussed these results and considered complete response to be an important outcome in sALCL, noting that the proportion of patients who experienced a complete response was substantial, especially in comparison to rates historically observed with therapies used to treat sALCL. The median duration of objective response was 12.6 months (13.2 months in updated analysis from April 2012) and the median duration of complete response was 13.2 months, which pERC considered evidence of a substantial clinical benefit. pERC also discussed that the length of progression-free survival of patients receiving brentuximab (13.3 months, 95%CI: 6.9 months to NE; 14.6 months, 95% CI, 6.9 to 20.6 months in updated analysis from April 2012) was longer than had been reported for the most recent prior treatment (HR=0.48, P=0.001). pERC considered that, in a population who has been previously treated, it was uncommon for progression-free survival to be longer than that observed for previous lines of chemotherapy. In addition, a substantial proportion of patients who received brentuximab were still alive one-year after starting treatment (71%, 95%CI: 57% to 80%, April 2012 analysis). Quality of life was not measured in the SG035-0004 study, although it was an outcome patient advocacy group input indicated was important. pERC considered these results and concluded that there is a net clinical benefit of treatment with brentuximab. However, pERC acknowledged that because of the non-randomized, non-comparative phase two study design, there was considerable uncertainty surrounding the exact magnitude of the benefit. pERC also discussed that there was additional uncertainty in the magnitude of benefit due to confounding from subsequent SCT in some patients, which may have resulted in improved outcomes for these patients. Therefore, pERC considered that prospective data collection to provide additional information on the magnitude of clinical benefit and the impact of subsequent SCT in this setting would be useful.

Safety: toxicity profile reasonable in this setting, peripheral neuropathy manageable

pERC discussed the safety of brentuximab based on adverse events reported in Study SG035-0004. The most common Grade 3 or 4 adverse events were peripheral sensory neuropathy (12%), neutropenia (21%), and thrombocytopenia (14%). pERC noted that the most common adverse event was peripheral neuropathy but that it was reversible in most patients after discontinuation of brentuximab. pERC noted that while progressive multifocal leukoencephalopathy (PML) was observed in three patients treated with brentuximab for Hodgkin lymphoma, no cases have been reported in patients with sALCL. However, pERC noted that only a small number of patients with sALCL have received brentuximab and PML could still be a concern as more patients are exposed to the drug. Although pERC considered it challenging to assess the safety of brentuximab in the absence of randomized comparative data, pERC concluded, based on available data, that the toxicity of brentuximab is manageable.

Need: aggressive disease with no effective, non-toxic treatment options

pERC noted that sALCL is an uncommon but aggressive malignancy and that the number of patients with sALCL is relatively small. Patients with sALCL who have relapsed or are refractory to chemotherapy are currently treated with non-curative approaches such as chemotherapy or radiation. Salvage chemotherapy regimens include gemcitabine-dexamethasone-cisplatin (GDP) or dexamethasone-high-dose AraC-cisplatin (DHAP), which are extremely toxic chemotherapy regimens and have limited effectiveness. Therefore, pERC agreed with the pCODR Clinical Guidance Panel that effective new agents with reduced toxicity are needed to treat sALCL.

PATIENT-BASED VALUES

Values of patients with sALCL: extending life and choice of effective treatment options

pERC discussed input from one patient advocacy group and concluded that brentuximab for the treatment of sALCL aligned with patient values. From a patient perspective, the availability of additional drug therapies for the treatment of sALCL, which enable the patient to have a choice in their therapy is an

important consideration. Therefore, pERC considered that providing patients with access to brentuximab would align with this value. In addition, patients want treatment options that will control their disease and extend their life, while also allowing them to enjoy a good quality of life. pERC noted in the SG035-0004 study, the proportion of patients alive at one year after receiving brentuximab was meaningful.

Patient values on treatment: tolerable side effects, improved quality of life

pERC noted that patients with sALCL have a high tolerance for risk and treatment side effects given the high relapse rates of sALCL, if the treatment offered is able to control their disease and improve quality of life. Patients also indicated that there is a significant unmet need for less toxic and more effective treatments for sALCL. pERC noted that the SG035-0004 study did not measure or report quality of life data. However, pERC discussed that a clinical benefit was observed based on improvements in progression-free survival, complete responses that were durable and one-year survival rates. Also, the toxicity profile of brentuximab appeared reasonable relative to the toxicities associated with chemotherapies to which this population would otherwise be exposed. pERC discussed that PML was a potential concern with brentuximab in sALCL given that 3 cases were observed in patients with Hodgkin lymphoma. No cases have been reported to date in sALCL and pERC and pERC concluded that the potential risk of PML would likely be an acceptable risk for patients who did not have other alternative therapeutic options. In general, pERC considered that brentuximab would provide patients with an effective treatment option in a setting where there are no effective, non-toxic therapies and that the side effects associated with brentuximab are tolerable. Therefore, pERC concluded that brentuximab in sALCL aligns with patient values.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility

The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness and cost-utility analysis of brentuximab compared to chemotherapy, with or without radiotherapy for patients with relapsed or refractory sALCL who had prior chemotherapy.

Basis of the economic model: clinical and economic inputs

Costs included drug acquisition and administration costs, costs of managing and treating adverse events, and downstream treatment with SCT and disease progression, where appropriate. Drug wastage was not incorporated into the submitted model although re-analyses conducted by the EGP adjusted for this.

Key clinical effects included progression-free survival and overall survival based on the non-comparative, non-randomized SG035-0004 study (for brentuximab) and observational registry data (for comparators). Literature-based utilities associated with complete response, stable or progressive disease and utility decrements from adverse events were also considered.

Drug costs: high absolute drug cost, wastage due to limited potential for vial sharing

At the list price, brentuximab costs $4,840.00 per 50mg vial. At the recommended dose of 1.8mg/kg every 3 weeks, the average cost, for a 70kg patient, per day in a 28-day course is $580.80 and the average cost per 28-day course is $16,262.40. Assuming wastage of the excess brentuximab, the average daily cost for a 70 kg patient is $691.43 and the average cost per 28-day course is $19,360. pERC recognized that the total cost for the treatment of a single patient could be as much as $232, 230 as brentuximab may be administered for up to 16 treatment cycles and approximately 3 vials would be required for each 3-week treatment cycle.

pERC noted that the price of brentuximab was a key driver of cost-effectiveness and that the cost per 28-day cycle of brentuximab was $16,262.40. pERC considered this absolute cost to be extremely high relative to other new high cost cancer drug treatments and that it is above and beyond typical costs. The Committee noted that in order to improve the cost-effectiveness of brentuximab and offset the considerable uncertainty in the incremental effect, a substantial reduction in drug price would likely be required. pERC also considered that any further prospective evidence regarding clinical efficacy that could be collected to decrease the uncertainty in the incremental effect would be of benefit in understanding the true cost-effectiveness of brentuximab.

pERC noted input from pCODR's Provincial Advisory Group on the potential for wastage because only 50 mg vials are available and the drug has only 24 hour stability following reconstitution. pERC noted that due to the small number of patients with sALCL who are relapsed or refractory following chemotherapy, vial sharing would be unlikely and therefore brentuximab wastage will be an issue for provinces to manage.

Cost-effectiveness estimates: substantial uncertainty in incremental effect and resulting estimates of cost effectiveness due to limitations of non-randomized, non-comparative data

pERC deliberated on the cost-effectiveness of brentuximab compared with chemotherapy with or without radiotherapy in patients with sALCL. It was noted that due to the limitations of relying on non-comparative, non-randomized evidence from Study SG035-0004, there was substantial uncertainty in the magnitude of the clinical benefit associated with brentuximab. pERC noted that the pCODR EGP's estimates of cost-effectiveness started at $130,398 per quality adjusted life year (QALY) but were likely substantially higher since these analyses were based on non-comparative data and the Panel was not confident in the incremental effect estimates that were derived from these data. In addition, there was substantial uncertainty surrounding the proportion of patients who would receive subsequent stem cell therapy and its impact on the cost-effectiveness of brentuximab. pERC noted that when equal rates of subsequent SCT were applied to the brentuximab and the comparator arm (28% each, based on 28% of brentuximab patients receiving subsequent SCT in the SG035-0004 study) the ICER was $148,843 per QALY and other scenarios resulted in higher cost-effectiveness estimates. The considerable uncertainty in the magnitude of clinical benefit of brentuximab led to a wide range of incremental cost-effectiveness estimates, all of which pERC considered unacceptable. Therefore, brentuximab could not be considered cost-effective at the submitted price.

pERC further noted that the price of brentuximab was a key driver of cost-effectiveness and that the absolute cost of brentuximab was extremely high relative to other cancer drug treatments. The Committee noted that in order to improve the cost-effectiveness of brentuximab and offset the considerable uncertainty in the incremental effect, a substantial reduction in drug price would likely be required. pERC also considered that the collection of more prospective data on the clinical benefit of brentuximab would reduce uncertainty on the magnitude of the benefit and improve the estimates of cost-effectiveness.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: potential drug wastage, increased chair time, potential for increased treatment cycles

pERC discussed input from pCODR's Provincial Advisory Group on the feasibility of implementing a funding recommendation for brentuximab and noted that several factors would be important to consider. pERC acknowledged a number of issues related to the cost of brentuximab and subsequent budget impact. pERC noted that due to the small number of patients with sALCL who relapse or become refractory to treatment after at least one prior chemotherapy regimen, the budget impact could be relatively small. However, because of the small patient population, vial sharing would be unlikely and, therefore, drug wastage could be an issue with brentuximab. pERC also noted that while each intravenous infusion requires only 30 minutes of chair time, overall, there would be an increase in the chair time required due to the number of treatment cycles relative to other chemotherapy protocols for patients with sALCL. pERC also noted that in Study SG035-0004, 21% of patients reported grade 3 or 4 neutropenia, and that the treatment and management of febrile neutropenia would incur additional costs.

DRUG AND CONDITION INFORMATION

Drug Information	• Chimeric monoclonal antibody that targets CD30 • 50 mg single-use vial • Recommended dose is 1.8 mg/kg, administered intravenously every 3 weeks
Cancer Treated	• Systemic anaplastic large cell lymphoma (sALCL) after failure of at least one multi-agent chemotherapy regimen.
Burden of Illness	• Uncommon and aggressive malignancy • Median age at onset of 34 years; 65% of patients present with advanced (stage III or IV) disease.
Current Standard Treatment	• For patients with relapsed chemotherapy-sensitive disease who are transplant-eligible, high-dose chemotherapy with autologous stem cell transplantation (HDT-ASCT) • For patients who have relapsed after HDT-ASCT or who are not eligible for HDT-ASCT, treatment is generally limited to non-curative approaches including gemcitabine-dexamethasone-cisplatin (GDP) or dexamethasone-high dose AraC-cisplatin (DHAP). • Single-agent alkylator-based regimens may be used in older, unfit patients.
Limitations of Current Therapy	• Limited effectiveness and substantial toxicity of multi-agent chemotherapy regimens

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 and Dr. Sunil Desai who were not present for the meeting

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 brentuximab vedotin (Adcetris) for systemic anaplastic large cell lymphoma, through their declarations,

no members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was 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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