pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

Erratum: This is a revised pERC Final Recommendation which supersedes the Final Recommendation for this drug and indication dated June 21, 2016. The revision was made to align the patient population in the pERC recommendation with the pivotal trial (ASPIRE).

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Carfilzomib (Kyprolis) **Submitted Funding Request:** In combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma following one prior treatment failure	
Submitted By: Amgen Canada Inc.	**Manufactured By:** Amgen Canada Inc.
NOC Date: January 15, 2016	**Submission Date:** December 11, 2016
Initial Recommendation: June 3, 2016	**Final Recommendation:** June 21, 2016 **Revised:** November 11, 2016

pERC RECOMMENDATION

pERC recommends reimbursement of carfilzomib (Kyprolis) in combination with lenalidomide and dexamethasone (Len-Dex) for patients with multiple myeloma who have received at least one prior treatment, on condition that the cost-effectiveness be improved to an acceptable level. Patients must not have had disease progression during treatment with bortezomib or if previously treated with lenalidomide and dexamethasone patients must not have

- discontinued therapy because of adverse effects,
- disease progression during the first 3 months of treatment, or
- progression at any time during treatment if lenalidomide plus dexamethasone was their most recent treatment.

Treatment should be in patients who have good performance status and are deemed to have adequate renal function. Treatment with carfilzomib should continue until disease progression or unacceptable toxicity, up to a maximum of 18 cycles.

The Committee made this recommendation because carfilzomib with Len-Dex demonstrated a net clinical benefit when compared with Len-Dex alone, based on a statistically significant and clinically meaningful improvement in progression-free survival, a trend toward an improvement in overall survival, a manageable toxicity profile, and at least maintenance in patient's quality of life. Carfilzomib plus Len-Dex also aligned with patient values.

However, pERC noted that carfilzomib plus Len-Dex could not be considered cost-effective compared with Len-Dex alone.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC was satisfied that there is a net clinical benefit with carfilzomib plus Len-Dex compared with Len-Dex alone, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of carfilzomib with Len-Dex.

Generalizability of results regarding Eastern Cooperative Oncology Group Performance Status and Renal Function
pERC noted that carfilzomib plus Len-Dex should be reimbursed for patients with a good performance status. pERC considered that patients with declining performance status (i.e. ECOG PS of 2 or more) may benefit from treatment with carfilzomib plus Len-Dex if the factors affecting performance status are myeloma-related and considered to be reversible with treatment. Additionally, although the trial was restricted to patients with creatinine clearance [CrCL] of greater than or equal to 50 mL/min, pERC agreed with the CGP that carfilzomib plus Len-Dex may be a reasonable option for select patients with CrCL < 50 mL/min, since carfilzomib is not excreted renally. However, these patients must be deemed clinically able to tolerate the requirement for the two hours of hydration that accompany carfilzomib administration. Furthermore, pERC recognized that dose adjustments for the Len-Dex component of the treatment may be required in the presence of compromised renal function. pERC also noted that the collection of prospective evidence would help confirm the efficacy and safety of administering carfilzomib plus Len-Dex in this patient population.

Time-Limited Need for Carfilzomib
At the time of implementing a funding recommendation for carfilzomib plus Len-Dex, jurisdictions may want to consider addressing the short-term, time-limited need for carfilzomib plus Len-Dex for patients who are currently receiving Len-Dex as a second-line therapy and have not experienced disease progression or intolerance during Len-Dex.

Optimal Sequencing of Carfilzomib plus Len-Dex and Other Therapies Unknown
pERC concluded that the optimal sequencing of carfilzomib plus Len-Dex and other treatments now available for the treatment of multiple myeloma is currently unknown. pERC was therefore unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces would need to address this issue upon implementation of carfilzomib reimbursement and noted that collaboration among provinces to develop a common approach would be of value.

Resource Use and Adoption Feasibility
pERC noted that the administration of carfilzomib is resource-intensive due to the frequency and changing pattern of dosing. Therefore pERC noted that jurisdictions will need to consider the incremental pharmacy and nursing resources involved.

SUMMARY OF pERC DELIBERATIONS

Despite significant advancement in the treatment and life expectancy of patients with multiple myeloma, it still remains an incurable disease and patients will relapse following initial therapy. While bortezomib- or lenalidomide-based therapies are currently the standard treatment options in the second-line setting, superiority of one over the other has not been conclusively demonstrated. Given that both options in the second-line setting have demonstrated an overall survival benefit, the choice of therapy largely depends on regimens used in the first line. pERC agreed that novel therapies that will further improve survival is a continued need for patients.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

The pCODR systematic review included one open-label randomized controlled trial, ASPIRE, that evaluated carfilzomib plus lenalidomide and dexamethasone (Len-Dex) compared with Len-Dex alone in patients with multiple myeloma who had disease relapse or progression on one to three prior treatments. pERC noted that there was a statistically significant improvement in independently assessed progression-free survival (PFS) in favour of the carfilzomib plus Len-Dex group with a median PFS of 26.3 versus 17.6 months in the Len-Dex alone group (hazard ratio [HR] = 0.69; 95% confidence interval [CI], 0.57 to 0.83, $P = 0.0001$). Although overall survival (OS) data were not yet mature, there was a trend in OS benefit in favour of the carfilzomib plus Len-Dex group compared with the Len-Dex alone group. pERC noted a minimal important difference for global health-related quality of life (HRQoL) in favour of carfilzomib plus Len-Dex at cycle 12, while the same measurement at other time points indicated no differences between arms. pERC therefore agreed that the impact of carfilzomib plus Len-Dex on patients' HRQoL was at least similar to Len-Dex alone. pERC discussed the toxicity profile of carfilzomib plus Len-Dex and noted that it was manageable. The Committee also noted that cardiac toxicity was a concern and that it occurred in a higher proportion of patients in the carfilzomib plus Len-Dex treatment group, particularly in the subset of patients older than 70 years of age. pERC therefore agreed that cardiac toxicities may be of specific concern in this population and will need to be monitored.

pERC discussed the eligibility criteria for treatment with carfilzomib plus Len-Dex and noted patients were not allowed into the trial if they had had disease progression during treatment with bortezomib. Patients previously treated with lenalidomide and dexamethasone were eligible so long as they did not discontinue therapy because of adverse effects, have disease progression during the first 3 months of treatment, or have progression at any time during treatment if lenalidomide plus dexamethasone was their most recent treatment. pERC therefore agreed that patients eligible for treatment with carfilzomib plus Len-Dex should meet these criteria. pERC also noted the Clinical Guidance Panel's (CGP's) conclusion that treatment decisions in current standard practice are not made on performance status alone, but also consider the manageability of toxicities and whether the patient's performance status is affected by myeloma-related factors. pERC agreed with the CGP's conclusion that patients with reversible myeloma-related Eastern Cooperative Oncology Group Performance Status (ECOG PS) > 2 may benefit from treatment with carfilzomib plus Len-Dex. pERC further discussed renal function as a criterion for treatment eligibility and the CGP's conclusion that carfilzomib plus Len-Dex should be available to patients with CrCl less than 50 mL/minute. pERC acknowledged that carfilzomib is not excreted renally; however, the specific concern for cardiac toxicities in combination with patients' ability to tolerate the 2 hours of hydration requirements that accompany carfilzomib administration remained a concern for the Committee. pERC therefore concluded that carfilzomib plus Len-Dex should be made available to patients with renal function considered adequate to tolerate the treatment-associated fluid loading. pERC also acknowledged the uncertainty in the magnitude of clinical benefit in these patients, and noted that the collection of prospective evidence would help confirm the efficacy and safety of administering carfilzomib plus Len-Dex in patients who have CrCl less than 50 mL/minute but whose renal function is considered adequate to tolerate the treatment-associated fluid load. Overall, pERC concluded that there is a net clinical benefit with carfilzomib plus Len-Dex based upon statistically significant and clinically meaningful improvements in PFS, a manageable toxicity profile, and at least stable quality of life (QoL) compared with Len-Dex.

pERC deliberated upon patient advocacy group input. pERC was pleased with the large number of respondents and proportion of patients with experience with carfilzomib. pERC agreed the input provided a balanced perspective of patients' experience and expectations and commended the quality of the input. pERC noted that patients valued having access to effective treatment options, improvements in QoL, and having a choice of therapies. pERC noted that the carfilzomib plus Len-Dex regimen aligns with the patient values of an effective treatment option that provides patients with a choice in therapy. pERC discussed the point that while QoL did not deteriorate in the trial, drug-related adverse events (AEs) needing to be managed may require an increase in clinic visits, which may not align with patient values of improved quality of life. pERC also discussed that the addition of an intravenous drug to a a combination (Len-Dex) that is otherwise orally administered may be challenging for some patients, as treatment would require frequent travel to clinics for the intravenous administration of carfilzomib. pERC also noted that the intense dosing schedule will be a barrier to accessibility to treatment for some patients. However, for patients who can manage the increase in visits, carfilzomib plus Len-Dex would align with patient values. pERC acknowledged and appreciated the balanced input provided by the patient advocacy group. Thus, although there may be some challenges for some patients in accessing treatment, pERC concluded that overall, carfilzomib plus Len-Dex aligned with patient values.

pERC deliberated upon the cost-effectiveness of carfilzomib plus Len-Dex compared with Len-Dex alone, which is the most relevant comparator in the Canadian context at the time of this review. pERC considered estimates provided by the submitter and reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP) and noted uncertainty regarding use of adjusted inputs for PFS and OS. pERC agreed with the EGP's use of the unadjusted analysis for PFS and OS inputs and noted that this had the largest impact on the incremental cost-effectiveness ratio (ICER). pERC deliberated upon the cost-effectiveness of carfilzomib plus Len-Dex compared with Len-Dex alone, which is the most relevant comparator in the Canadian context at the time of this review. pERC considered estimates provided by the submitter and reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP). With regard to the options presented in the submitted model, one based on the ITT analysis and one with adjustment for baseline covariates, pERC agreed with the EGP's position that there is uncertainty inherent in results based on post-hoc non-protocol-defined adjustment for baseline covariates, particularly when the adjustment for covariates produces results that are different from the ITT analysis. Additionally, pERC noted that the adjusted data have not been peer-reviewed nor published, further adding to the uncertainty of the data. Therefore pERC accepted the EGP's reanalysis estimates using the unadjusted ITT analysis, which is based on randomised data that have been peer-reviewed and published. pERC also acknowledged that smaller vial sizes may become available for carfilzomib in the near future but noted that at the time of the review, only the 60mg vial size was available. pERC therefore supported the EGP's use of the 60mg package and wastage associated with this vial given this is the vial currently available to jurisdictions. pERC further noted that the ASPIRE trial did not demonstrate a statistically significant OS benefit between arms. Despite this, the submitted model projected an OS benefit in the progression free and post progression states. pERC accepted that setting the HR to 1 at 42 months was a reasonable approach to mitigate the uncertainty in post progression benefit. The re-analysis estimates still captured 0.539 LY gained in the progression free state. pERC agreed with the EGP's approach as it accounts for the possibility of an OS benefit, although the clinical trial has not demonstrated a statistically significant OS benefit to date. When combining the use of the ITT analysis, changes to inputs for wastage, removing the post-progression benefit accrued, and increasing administration cost to better reflect clinical practice, the incremental cost-effectiveness ratio (ICER) increased dramatically. pERC agreed that the true ICER is likely at the higher end of the EGP's range. Therefore pERC, concluded that carfilzomib plus Len-Dex is not cost-effective. Additionally pERC discussed that the submitted budget impact estimates did not fully convey the true budget impact of one high cost combination therapy compared to another high cost regimen, and may artificially mask the true budget impact of carfilzomib plus Len-Dex.

pERC considered the feasibility of implementing a reimbursement recommendation for carfilzomib plus Len-Dex. Given that the available evidence excludes patients who had progression on Len-Dex or within 60 days of treatment with Len-Dex if it was the last treatment received, or intolerance to lenalidomide, the use of carfilzomib plus Len-Dex in patients who have had Len-Dex in a prior setting will be limited. pERC also noted that there is no evidence for the use of carfilzomib in the front-line setting; nor is there evidence for use of carfilzomib following progression on Len-Dex, outside of the inclusion criteria specified in the ASPIRE trial. pERC therefore acknowledged that the use of carfilzomib plus Len-Dex will be limited if/when Len-Dex is reimbursed in front-line setting. pERC noted that the budget impact analysis is sensitive to number of eligible patients, market uptake, wastage, and drug costs.

At this time, pERC could not comment on the efficacy and safety of carfilzomib plus Len-Dex in patients who are currently on maintenance therapy with bortezomib or Len-Dex post–stem cell transplant, given that there is no evidence for the use of carfilzomib plus Len-Dex in this population. pERC also noted that there is no evidence to support or refute the use of carfilzomib plus Len-Dex in patients who have progressed following lenalidomide monotherapy, in the maintenance setting. The Committee was therefore unable to draw any conclusion on the clinical benefit of using carfilzomib plus Len-Dex in this patient population. The Committee, however, agreed that if patients have received maintenance therapy with lenalidomide, and are no longer on maintenance treatment, but still meet the trial eligibility criteria, they should be eligible for carfilzomib plus Len-Dex. pERC further noted that there are likely very few instances where patients received Len-Dex in a prior line and who would then qualify for carfilzomib plus Len-Dex. pERC also was unable to make an evidence-informed recommendation on the optimal sequencing of treatments in this setting, given the lack of evidence for sequencing. However, pERC recognized that provinces would need to address this issue upon implementation of carfilzomib plus Len-Dex funding and noted that collaboration among provinces to develop a common approach would be of value.

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 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 (Myeloma Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- one patient advocacy group (Myeloma Canada)
- the Submitter (Amgen Inc.)

The pERC Initial Recommendation was to reimbursement carfilzomib (Kyprolis) in combination with lenalidomide and dexamethasone (Len-Dex) for patients with multiple myeloma following failure of one prior treatment, on condition that the cost-effectiveness be improved to an acceptable level.

Feedback on the pERC Initial Recommendation indicated that the manufacturer agreed in part with the pERC Initial Recommendation and pCODR's Provincial Advisory Group agreed with the pERC Initial Recommendation. The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy carfilzomib plus lenalidomide and dexamethasone (Len-Dex) in the treatment of patients following one prior treatment failure.

Studies included: One open-label randomized controlled trial

The pCODR systematic review included one open-label randomized controlled trial, ASPIRE, which randomized 792 patients with relapsed multiple myeloma to receive carfilzomib plus Len-Dex (n = 396) or Len-Dex alone (n = 396). Carfilzomib was given up to cycle 18. In both groups, Len-Dex was given until disease progression, withdrawal of consent, or occurrence of unacceptable toxic effects.

Patient populations: Ineligible if intolerant or refractory to lenalidomide or bortezomib

Baseline characteristics were well balanced between groups. The median age of patients in the ASPIRE study was 64.0 years and nearly 30% of patients in both arms were older than 70 years. The majority of patients in the trial had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (42.9%) or 1 (47.6%), while 9.5% of patients in both groups had an ECOG PS of 2. Patients also had received a median of two previous therapies. Overall, 65.8% had received bortezomib, 19.8% had received lenalidomide, and 56% had received prior transplant.

pERC discussed the eligibility criteria for the trial and noted patients were not allowed into the trial if they had had disease progression on bortezomib. Patients previously treated with lenalidomide and dexamethasone were eligible so long as they did not discontinue therapy because of adverse effects, have disease progression during the first 3 months of treatment, or have progression at any time during treatment if lenalidomide plus dexamethasone was their most recent treatment. pERC therefore agreed that patients eligible for treatment with carfilzomib plus Len-Dex should meet these criteria. Additionally, if patients have received maintenance therapy with lenalidomide, but still meet these criteria, they would be eligible for carfilzomib plus Len-Dex. pERC further noted that there are likely very

few instances where patients would have had Len-Dex in a prior line and would then qualify for carfilzomib plus Len-Dex. Additionally, pERC noted that the number of patients eligible for treatment with the carfilzomib plus Len-Dex will be limited if Len-Dex becomes available as a first-line treatment. However, there are no data on the use of carfilzomib plus Len-Dex in first-line treatment of patients with multiple myeloma.

pERC also noted the pCODR Clinical Guidance Panel's (CGP's) conclusion that treatment decisions in current standard practice are not made on performance status alone, but also consider the manageability of toxicities and whether the patient's performance status is affected by myeloma-related factors. pERC therefore agreed with the CGP's conclusion that patients with reversible myeloma-related ECOG PS greater than 2 may benefit from treatment with carfilzomib plus Len-Dex. pERC also discussed renal function as a criterion for treatment eligibility. pERC acknowledged that carfilzomib is not excreted renally; however, the specific concern for cardiac toxicities in combination with patients' ability to tolerate the 2 hours of hydration requirements that accompany carfilzomib administration remained a concern for the Committee. pERC therefore concluded that carfilzomib plus Len-Dex should be made available to patients with renal function considered adequate to tolerate the treatment-associated fluid loading. pERC also acknowledged the uncertainty in the magnitude of clinical benefit in these patients, and noted that the collection of prospective evidence would help confirm the efficacy and safety of administering carfilzomib plus Len-Dex in patients who have CrCl less than 50 mL/minute but are considered to have renal function adequate to tolerate the treatment-associated fluid load.

Key efficacy results: Clinically meaningful progression-free survival benefit

The primary end point of the ASPIRE trial, and thus the key efficacy outcome deliberated upon by pERC, was progression-free survival (PFS). pERC noted that there was a statistically significant and clinically meaningful improvement in PFS reported in favour of the carfilzomib plus Len-Dex group with a 31% reduction in the risk of progression or death during the study period. Median PFS was 26.3 versus 17.6 months in the carfilzomib plus Len-Dex and Len-Dex groups, respectively (hazard ratio [HR] = 0.69; 95% confidence interval [CI], 0.57 to 0.83; *P* = 0.0001). For secondary outcomes, 24-month survival rates were 73.3% and 65.0% in the carfilzomib plus Len-Dex and Len-Dex groups, respectively. pERC noted that a post-hoc subgroup analysis in patients aged 70 years and older demonstrated a similar benefit in this population that is more reflective of that expected in clinical practice. In these older patients, median PFS was 23.8 months versus 16.0 months in the carfilzomib plus Len-Dex and Len-Dex groups, respectively (HR = 0.74; 95% CI, 0.513-1.065, *P* = 0.0521). Median overall survival (OS) was not reached in either arm, but a trend was present toward a benefit with carfilzomib plus Len-Dex. The 24-month OS rate was 73.3% and 65.0% in the carfilzomib plus Len-Dex control groups, respectively.

Quality of life: At least similar QoL between treatment groups

Using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core Module (QLQ-C30), a minimally important difference was measured only at cycle 12. Measurements at other time points (cycles 3, 6, and 18) indicated no differences between arms. pERC discussed these results and agreed that the impact of carfilzomib plus Len-Dex on patients' health-related quality of life (HRQoL) was at least similar to that of the Len-Dex regimen. pERC noted that improvement in quality of life (QoL) was an important outcome to patients and input from patients, using a rating system from 1 (poor quality of life) to 5 (excellent quality of life), indicated that some patients experienced "excellent quality of life" with carfilzomib. pERC acknowledged that caution is to be used when interpreting this scale, as the Committee was not aware whether it was appropriately validated.

Safety: Concern for cardiac toxicity

pERC discussed the toxicity profile of carfilzomib plus Len-Dex and noted that the side effects were generally manageable. The overall occurrence of grade 3 to 4 adverse events (AEs) was similar between treatment groups. Grade 3 or higher cardiac failure rate were higher in the carfilzomib plus Len-Dex compared with Len-Dex (3.8% compared with 1.8%). In a post-hoc subgroup analysis of patients older than 70 years in the ASPIRE trial, the rate of heart failure was 8.7% and 1.8% in the carfilzomib plus Len-Dex and Len-Dex groups, respectively. pERC therefore agreed that cardiac toxicities may be of some concern in this population and will need to be monitored.

Need: Novel agents with improved survival

Despite significant advancement in the treatment and life expectancy of patients with myeloma, it still remains an incurable disease. In 2015, it was expected that approximately 2,700 new cases would be diagnosed in Canada and 1,400 patients would die of the disease. Regardless of the initial therapy,

patients with myeloma will relapse and further therapy will be required. Second-line therapy using either a bortezomib- or lenalidomide-based therapy has been standard of care, and choice of therapy largely depends on which regimen was not used in the first-line setting. Superiority of one regimen over the other is unknown, and regardless of therapy used, life expectancy is limited. Finding novel therapies that can improve life expectancy is a continued need. Using newer chemotherapies in combination, such as carfilzomib, lenalidomide, and dexamethasone, may lead to improvement in outcomes. Carfilzomib plus Len-Dex is a novel combination, and the first regimen to be compared with the standard second-line therapy of lenalidomide and dexamethasone, in the relapsed setting. In discussing the eligible patient population, pERC noted that few patients who have had lenalidomide in prior regimens would be eligible to receive carfilzomib plus Len-Dex. pERC also noted that with the potential shifting of Len-Dex to the front-line setting, the use of carfilzomib plus Len-Dex in subsequent lines of therapy will be limited.

PATIENT-BASED VALUES

Values of patients with multiple myeloma: Treatment options, symptom control, quality of life improvement

pERC reviewed input from one patient advocacy group and noted the large number of patients who had completed their patient survey. Symptoms most important to control were infections, followed by kidney problems, pain, mobility, neuropathy, fatigue, shortness of breath, mood and/or emotional issues, and stomach issues, including diarrhea, nausea, and gastrointestinal. Patients also reported that their disease limited their ability to work the most, followed by ability to travel, exercise, volunteer, conduct household chores, fulfill family obligations, and spend time with family.

Given the impact of the disease on patients' QoL, patients valued access to effective treatments, the ability to choose between effective treatment options based on their side effect profile and have options that improve QoL and physical condition. Most patients indicated a willingness to tolerate some side effects with new effective treatments. pERC concluded that the results of the ASPIRE trial align with the patient value of having additional effective treatment options. However, pERC noted that the intravenous route of administration and intense dosing schedule will require that patients frequently travel to a chemotherapy clinic or hospital to access carfilzomib.

pERC was also pleased with large number of respondents and proportion of patients with experience with carfilzomib. pERC agreed the input provided a balanced perspective of patients' experience and expectations and commended the quality of the input.

Patient values on treatment: Manageable side effects; anticipating an extension in remission

The most frequently experienced side effects of currently available treatments were reported to be fatigue, followed by neuropathy, pain, insomnia, stomach issues, nausea, shortness of breath, and confusion.

Forty-six patients reported experience with carfilzomib. More than half of the patients reported that the side effects of carfilzomib were tolerable. The most common side effects were nausea, fever, pneumonia, diarrhea, shortness of breath, neutropenia, anemia, thrombocytopenia, and fatigue. Using a rating system from 1 (poor quality of life) to 5 (excellent quality of life), input from patients with direct experience using carfilzomib indicated that some patients experienced "excellent quality of life" with carfilzomib. pERC acknowledged that caution is to be used when interpreting this scale as the Committee was not aware whether it was appropriately validated. Most patients also indicated having had a positive experience with carfilzomib, with many anticipating extension of their remission period. Based on data from ASPIRE, pERC noted that improvements in QoL were measured only at one cycle in the ASPIRE trial, with the remainder of treatment periods demonstrating at least similar QoL between treatment groups.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness analysis and cost-utility analysis comparing carfilzomib plus Len-Dex with Len-Dex alone for the treatment of patients with previously treated multiple myeloma.

Basis of the economic model: Most clinical inputs based on pivotal trial, post-hoc adjustment of efficacy inputs

Costs considered in the analysis included drug acquisition, drug administration, AE management, end-of-life costs, and other health care costs (i.e., monitoring).

The clinical effects considered in the analysis were based on survival estimates from the ASPIRE trial, treatment discontinuation and AEs also based on the ASPIRE trial, and AEs associated with subsequent treatments based on other trials. pERC noted that inputs for PFS and OS were based on post-hoc analysis that adjusted the results for baseline factors which the submitter noted were associated with the outcomes of interest. pERC agreed with the EGP's use of the intention-to-treat analysis for PFS and OS inputs. pERC noted that there is uncertainty in using results based on post-hoc non-protocol specified adjustment of baseline covariates, particularly when the adjustment for covariates produces results that are different from the ITT analysis. Additionally, pERC noted that the adjusted data, used in the submitter's base case results, have not been peer-reviewed or published. Therefore pERC re-iterated its support of the EGP's reanalysis estimates using the unadjusted ITT analysis which are based on randomised data that have been peer-reviewed and published.

Drug costs: High-cost drug combinations

At the list price, carfilzomib costs $1,533.33 per single-use vial of 60 mg.

- For cycle 1, at the recommended starting dose of 20 mg/m^2 on days 1 and 2 and target dose of 27 mg/m^2 thereafter (days 8, 9, 15, and 16), carfilzomib costs $229.63 per day and $6,429.76 per 28 days. When wastage is considered, carfilzomib costs $273.81 per day and $7,666.65 per 28 days.
- For cycles 2 to 12, at the recommended dose of 27 mg/m^2 on days 1, 2, 8, 9, 15, and 16, carfilzomib costs $251.36 per day and $7,037.98 per 28 days. When wastage is considered, carfilzomib costs $273.81 per day and $7,666.65 per 28 days.
- For cycles 13 to 18, at the recommended dose of 27 mg/m^2 on days 1, 2, 15, and 16, carfilzomib costs $167.57 per day and $4,691.99 per 28 days. When wastage is considered, carfilzomib costs $219.05 per day and $6,133.32 per 28 days.

pERC acknowledged that smaller vial sizes may become available for carfilzomib in the near future but noted that at the time of the pCODR review, only a 60mg vial size was available. pERC therefore supported the EGP's use of the 60mg package and wastage associated with this vial given this is the vial currently available to jurisdictions.

At the list price, lenalidomide costs $340.00, $361.00, $382.00, $403.00, and $424.00 per 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg capsule, respectively. At the recommended dose of 25 mg orally on days 1 to 21 per 28-day cycle, lenalidomide costs $318.00 per day and $8,904.00 per 28-day cycle. At the list price, dexamethasone costs $3.00 per 40 mg orally. At the recommended dose of 40 mg per day on days 1, 8, 15, and 22 of a 28-day cycle, dexamethasone costs $0.44 per day and $12.18 per 28 days.

pERC discussed the cost of carfilzomib and noted that jurisdictions will need to consider the budgetary impact of making this drug available. pERC noted that carfilzomib will be combined with an already expensive regimen and agreed that a substantial reduction in the cost of carfilzomib is needed to manage the budgetary impact.

Cost-effectiveness estimates: Comparison between two high-cost drugs; intention-to-treat analysis

pERC deliberated upon the cost-effectiveness of carfilzomib plus Len-Dex compared with Len-Dex alone, based on the submitted economic evaluation and reanalysis estimates provided by the EGP. Several uncertainties were highlighted by the EGP. Given that inputs for PFS and OS were based on post-hoc analysis that adjusted the results for baseline factors associated with the outcomes of interest, pERC agreed with the EGP's use of the intention-to-treat analysis for PFS and OS inputs. This change had the largest impact on the incremental cost-effectiveness ratio (ICER). pERC noted that there is uncertainty in using results based on post-hoc non-protocol specified adjustment of baseline covariates particularly when the adjustment for covariates produces results that are different from the ITT analysis. Additionally, pERC noted that the adjusted data, used in the submitter's base case results, have not been peer-reviewed or published. Given this uncertainty, pERC supported the EGP's use of the ITT results for their re-analysis estimates. Additionally, given the lack of clinical rationale to support the presence of post-progression benefit in the carfilzomib arm and the uncertainty of the ongoing relative benefit of carfilzomib beyond trial period, pERC agreed with the the exploration of reducing the hazard ratio to 1

beyond 42 months (trial period). pERC noted that the ASPIRE trial did not demonstrate an OS benefit between arms. Despite this, the submitted model projected OS benefit in the progression free and post progression states, neither of which are supported by clinical evidence. pERC further noted that setting the HR to 1 only at 42 months was a reasonable approach given that it removes the post progression benefit and still captured 0.539 LY gained in the progression free state. pERC was satisfied with the EGP's approach of removing only the post progression benefit. When combining these changes with modifications to inputs for wastage and increasing administration cost to better reflect clinical practice, the ICER increased to $270,652 to $347,640. pERC agreed that the true ICER is likely at the higher end of the range. Additionally, pERC noted that the submitted analysis and EGP's reanalysis estimates reflect an ICER of one high-cost combination therapy to another high-cost regimen, which may artificially mask the true cost impact of carfilzomib plus Len-Dex. pERC, therefore, concluded that carfilzomib plus Len-Dex is not cost-effective. Additionally pERC discussed that the submitted budget impact estimates did not fully convey the true budget impact of one high cost combination therapy compared to another high cost regimen, and may artificially mask the true budget impact of carfilzomib plus Len-Dex.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Limited application when Len-Dex use in front line begins

pERC considered the feasibility of implementing a funding recommendation for carfilzomib plus Len-Dex. pERC discussed several barriers to accessibility that patients may experience with carfilzomib. As an intravenous treatment, carfilzomib will require that patients travel to chemotherapy clinics or hospitals for treatment. Although infusion times are 10 minutes long, patients may also have lengthy (> 2 hours) pre- and post-treatment hydration. pERC also noted that the multiple and intense dosing schedule (two consecutive days weekly for three weeks out of four in the first 12 cycles) with carfilzomib will be challenging for scheduling chemotherapy chair time and for patients to travel to receive therapy, and would introduce incremental work load for pharmacy staff. pERC agreed with the CGP and concluded that dose adjustments should be based on established protocols (typically, weight change of 5%) as opposed to what is recommended in the clinical trial (weight change of 20%).

pERC discussed potential interest in using carfilzomib in the front-line setting in combination with Len-Dex or in patients who have recently progressed following first-line Len-Dex . pERC noted that there is no evidence for the use of carfilzomib in the front-line setting, nor is there evidence for use of carfilzomib following progression on Len-Dex, outside of the inclusion criteria specified in the ASPIRE trial. pERC further acknowledged that the use of carfilzomib plus Len-Dex will be limited if/when Len-Dex is reimbursed in the front line setting. The use of carfilzomib plus Len-Dex in patients who have had Len-Dex in prior settings will be limited; the available evidence excludes patients who had progression on Len-Dex or within 60 days of treatment with Len-Dex if it was the last treatment received or intolerance to lenalidomide. pERC noted that the budget impact analysis is sensitive to number of eligible patients, market uptake, wastage and drug costs.

pERC cannot comment on the efficacy and safety of carfilzomib plus Len-Dex in patients who are on maintenance therapy with bortezomib or lenalidomide post–stem cell transplant, given that there is no evidence for the use of carfilzomib in these scenarios. pERC noted that there is no evidence to support or refute the use of carfilzomib plus Len-Dex in patients who have progressed following lenalidomide monotherapy in the maintenance setting and was therefore unable to draw any conclusion on the clinical benefit of using carfilzomib plus Len-Dex in this patient population. The optimal sequencing of carfilzomib plus Len-Dex and other treatments now available for the treatment of multiple myeloma is currently unknown. pERC was therefore unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces would need to address this issue upon implementation of carfilzomib funding and noted that collaboration among provinces to develop a common approach would be of value. pERC noted that the administration of carfilzomib is resource-intensive. Therefore, pERC noted that jurisdictions will need to consider the incremental costs associated with pharmacy and nursing resources for carfilzomib due to the resource intensive nature of the dose preparation and frequent dosing schedule, all of which may require significant output of cost and human resources.

DRUG AND CONDITION INFORMATION

Drug Information	• Second-generation proteasome inhibitor • Single-use vial of 60 mg • Cycle 1: starting dose, 20 mg/m^2 on days 1 and 2; target dose, 27 mg/m^2 thereafter on days 8, 9, 15, and 16 • Cycles 2 to 12: 27 mg/m^2 on days 1, 2, 8, 9, 15, and 16 • Cycles 13 to 18: 27 mg/m^2 on days 1, 2, 15, and 16
Cancer Treated	• Multiple myeloma
Burden of Illness	• 2,700 Canadians diagnosed, and 1,400 patients will die of this disease in 2015 • Despite significant advancement, remains an incurable disease
Current Standard Treatment	• Lenalidomide and dexamethasone
Limitations of Current Therapy	• Life expectancy is limited with current therapies • Continued need for novel therapies that can improve life expectancy

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Carole McMahon, Patient Member
Dr. Catherine Moltzan, Oncologist
Valerie McDonald, Patient Member Alternate
Jo Nanson, Patient Member
Karen MacCurdy-Thompson, Pharmacist
Danica Wasney, Pharmacist

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

- Matthew Cheung and Jo Nanson, who were not present for the meeting.

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

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 carfilzomib (Kyprolis) plus lenalidomide and dexamethasone for multiple myeloma through their declarations, four 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

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 pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

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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