pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

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

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Carfilzomib (Kyprolis)	
Submitted Funding Request: In combination with dexamethasone alone in the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy	
Submitted By: Amgen Canada Inc.	**Manufactured By:** Amgen Canada Inc.
NOC Date: November 22, 2016	**Submission Date:** September 9, 2016
Initial Recommendation: February 2, 2017	**Final Recommendation:** March 30, 2017

pERC RECOMMENDATION	pERC recommends reimbursement of carfilzomib (Kyprolis) in combination with dexamethasone (Dex) for patients with relapsed multiple myeloma with a good performance status who have received one to three prior treatments, on the condition that the cost-effectiveness be improved to an acceptable level. The Committee made this recommendation because carfilzomib plus Dex demonstrated a net clinical benefit when compared with bortezomib plus Dex, based on a statistically significant and clinically meaningful improvement in progression-free survival (PFS), a trend toward an improvement in overall survival (OS), and at least maintenance in patients' quality of life (QoL). The Committee acknowledged that carfilzomib plus Dex is associated with manageable but not insignificant toxicity. The committee felt that carfilzomib plus Dex also aligned with patient values. However, pERC noted that, at the submitted price, carfilzomib plus Dex could not be considered cost-effective compared with bortezomib plus Dex.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Generalizability of Results Regarding Eastern Cooperative Oncology Group Performance Status** pERC noted that carfilzomib plus Dex should be reimbursed for patients with a good performance status. pERC considered that patients with declining performance status (i.e., Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 2 or more) may benefit from treatment with carfilzomib plus Dex if the factors affecting performance status are myeloma-related and are considered to be reversible with treatment. **Use of Carfilzomib as a Triplet Versus Doublet Therapy** pERC recently recommended the reimbursement of carfilzomib as a triplet therapy in combination with lenalidomide and Dex based on the results of the ASPIRE trial. Given the likely forthcoming availability of this triplet therapy, pERC discussed at length the place in therapy of carfilzomib plus Dex. pERC acknowledged clinical opinion that suggested Canadian treatment practice in multiple myeloma is moving toward triplet therapy;

therefore, the triplet therapy would be the preferred option. However, pERC acknowledged the existence of a distinct population of patients who would be eligible for the doublet therapy with carfilzomib plus Dex. In particular, patients who have previously been treated with lenalidomide and are no longer eligible for the triplet therapy, as well as older patients who have pre-existing conditions making them ineligible for the triplet therapy (i.e., impaired renal function). pERC therefore agreed that the two treatment regimens would not be used in sequence as there would not be a scenario in which patients would be eligible for both the triplet and doublet therapy.

Optimal Sequencing of Carfilzomib Plus Dex and Other Therapies Unknown

pERC concluded that the optimal sequencing of carfilzomib plus 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. pERC acknowledged that carfilzomib plus Dex would be an alternative therapy for patients who are ineligible to receive triplet therapy and not an add-on to the existing sequence of treatments.

Time-Limited Need for Relapsed Patients Who Are Currently on Bortezomib-Based Treatment

At the time of implementing a reimbursement recommendation for carfilzomib plus Dex, jurisdictions may want to consider addressing the short-term, time-limited need for carfilzomib plus Dex for patients with relapsed myeloma and who are currently receiving a bortezomib-based regimen.

Pricing Arrangements to Improve Cost-Effectiveness

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

Resource Use and Adoption Feasibility

pERC noted that the frequency of administration and changing pattern of dosing is resource intensive. Therefore, pERC noted that jurisdictions will need to consider the incremental pharmacy and nursing resources involved.

SUMMARY OF pERC DELIBERATIONS

Despite significant advancements in the treatment and life expectancy of patients with multiple myeloma, it still remains an incurable disease and patients will relapse following initial therapy. Bortezomib- or lenalidomide-based therapies are currently the standard treatment options in the second-line setting; however, superiority of one regimen over the other has not been conclusively demonstrated. Given that both options in the second-line setting have demonstrated an OS benefit, the choice of therapy largely depends on regimens used in the first line. In the first-line setting, younger patients (i.e., < 70 years) may also be eligible for bortezomib-based induction followed by autologous stem cell transplant followed by maintenance low-dose lenalidomide. Recently, carfilzomib in combination with lenalidomide and Dex has been recommended for reimbursement in the relapsed setting. pERC noted that all patients may not be eligible for the triplet therapy, as eligibility will depend on patients' age, prior treatment history, and pre-existing conditions (e.g., renal function). pERC therefore agreed that novel therapies that further improve survival are a continued need for these patients.

pERC's *Deliberative Framework* for drug reimbursement 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, ENDEAVOR, that evaluated carfilzomib plus Dex compared with bortezomib plus Dex in patients with relapsed or refractory multiple myeloma who have had one to three prior treatments. pERC noted that there was a statistically significant improvement in PFS in favour of the carfilzomib plus Dex group, with a median PFS of 18.7 versus 9.4 months in the bortezomib plus Dex group (hazard ratio [HR] = 0.53; 95% confidence interval [CI], 0.44 to 0.65; $P < 0.0001$). The absolute magnitude of difference (9.3 months) was considered to be meaningful in this patient population. Although OS data were not yet mature, pERC agreed that at the 3 year updated analysis there was a trend in OS benefit in favour of the carfilzomib plus Dex group compared with the bortezomib plus Dex group. A greater proportion of patients in the carfilzomib plus Dex group also achieved objective response, including complete and very good partial response. pERC considered that depth of response in multiple myeloma to possibly be associated with a survival benefit. On average, patients in the carfilzomib plus Dex group had a numerically better global health status and/or QoL compared with patients in the bortezomib plus Dex group; however, the minimal important difference was not met. pERC therefore agreed that the impact of carfilzomib plus Dex on patients' health-related QoL was at least similar to that of patients receiving bortezomib plus Dex. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer related to additional results on the patient-reported outcomes (PROs) provided within the feedback. pERC noted that the information in the manufacturer's feedback suggested that minimal important differences (MIDs) were met at two time points for global health status and were approached at two other measurement points. A review of the feedback by the Methods team indicated that these data were not available during the review, as only limited data were available on patient-reported outcomes. Given the limited information available on patient-reported outcomes, the lack of any statistical analysis to support that differences may exist, and the exploratory nature of patient-reported outcomes in the trial, pERC agreed that caution should be used in interpreting the results within the feedback document. pERC discussed the toxicity profile of carfilzomib plus Dex and noted the increase in the occurrence of grade 3 adverse events and grade 3 serious adverse events among patients in the carfilzomib plus Dex group. The Committee also noted that cardiac toxicity occurred in a higher proportion of patients in the carfilzomib plus Dex treatment group. pERC therefore agreed that cardiac toxicities continue to be a specific concern in this population and need to be monitored. Overall, pERC concluded that the toxicity profile was manageable, although not insignificant.

pERC discussed the eligibility criteria for treatment with carfilzomib plus Dex, particularly as related to patients who would be eligible for the triplet therapy with carfilzomib plus lenalidomide and Dex, a treatment regimen that was recently reviewed and recommended for reimbursement by pERC. In considering that the patient populations are overlapping between the ASPIRE and ENDEAVOR trials, the Committee agreed with the Clinical Guidance Panel's (CGP's) opinion, which noted that the triplet therapy is the preferred option for patients deemed to be eligible. Based on the ASPIRE trial and pERC's reimbursement recommendation for the carfilzomib plus lenalidomide and Dex regimen, patients were

eligible for the triplet therapy if they had not previously progressed during treatment with bortezomib. Additionally, patients previously treated with lenalidomide and Dex were eligible for the triplet therapy so long as they did not discontinue therapy because of adverse effects, have disease progression during the first three months of treatment, or have progression at any time during treatment if lenalidomide plus Dex was their most recent treatment. Therefore, pERC acknowledged that patients who would be ineligible for treatment with the triplet therapy should be considered for treatment with carfilzomib plus Dex. This would include, and is not limited to, patients who have previously progressed on lenalidomide plus Dex, patients who have received maintenance lenalidomide treatment and do not meet the eligibility criteria for the triplet therapy, and older patients with pre-existing conditions precluding them from receiving the triplet therapy (e.g., impaired renal function). pERC further noted that lenalidomide is considered to be a treatment that is difficult to tolerate for patients with impaired renal function, while proteasome inhibitors have demonstrated a better toxicity profile in this population. pERC therefore agreed that the two treatment regimens would not be used in sequence as there would not be a scenario in which patients would be eligible for both the triplet and double therapy. Therefore, carfilzomib plus Dex is an alternative therapy for patients who are ineligible for the triplet therapy. At this time, pERC could not comment on the efficacy and safety of carfilzomib plus Dex in patients who were previously refractory to bortezomib treatment. Having considered the limitations associated with drawing a conclusion based on a small subgroup of patients, the Committee agreed that clear evidence would be needed to determine whether the use of a newer proteasome inhibitor in patients refractory to bortezomib would be reasonable. pERC also agreed with the CGP's conclusion that patients with reversible myeloma-related ECOG PS > 2 may benefit from treatment with carfilzomib plus Dex. Patients older than 70 years were also included in the ENDEAVOR trial and the Committee agreed that the overall trial results are generalizable for this population. However, pERC agreed with the CGP's caution that there may be an increased risk of heart failure in older patients; therefore, further study is necessary to clarify this risk. Overall, pERC concluded that there is a net clinical benefit with carfilzomib plus Dex based upon statistically significant and clinically meaningful improvements in PFS, a manageable but not insignificant toxicity profile, and at least stable QoL compared with bortezomib plus Dex.

pERC deliberated upon patient advocacy group input and noted that patients valued having access to effective treatment options, maintenance, or improvement in QoL; having a choice of therapies; and managing disease- and treatment-related symptoms. pERC noted that the results of the ENDEAVOR trial demonstrated that carfilzomib plus Dex provides improvements in PFS and at least maintenance of QoL, results that align with the patient value of having access to an effective treatment option. However, pERC noted that grade 3 or higher adverse events and serious adverse events were higher in the carfilzomib group. pERC agreed that these side effects were manageable, but nonetheless they were not insignificant, as patients expressed value in having additional treatment options that better managed their disease symptoms and had a manageable toxicity profile. 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 Dex would align with patient values. Overall, pERC agreed that carfilzomib plus Dex aligned with patient values.

pERC deliberated upon the cost-effectiveness of carfilzomib plus Dex compared with bortezomib plus Dex. pERC considered uncertainties in model inputs addressed by the Economic Guidance Panel (EGP) and agreed that the model time horizon had the largest impact on the incremental cost-effectiveness ratio (ICER). pERC accepted CGP input and highlighted the improbability of expecting a 20-year time horizon in patients with relapsed multiple myeloma who have a median age of 70 years at diagnosis, most of whom will have had several lines of treatment prior to carfilzomib-based therapy. pERC therefore accepted the EGP's use of a 10-year time horizon. In addition, the use of utilities from the trial rather than utilities from the literature, adjusted based on the trial data, and the modelling of once-weekly bortezomib dosing substantially affected the ICER. pERC considered the clinical rationale for both of these inputs and accepted the changes made by the EGP. The EGP's reanalyses estimates also included modifications to the time spent on subsequent treatments and the method for extrapolating the OS data. pERC noted that these two parameters had less of an impact on the ICER. Overall, pERC agreed that carfilzomib plus Dex is not cost-effective, whether considering the submitted base-case results or the EGP's range of reanalysis estimates.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer criticizing the use of a 10-year time horizon and once-weekly dosing of bortezomib in the EGP's reanalyses estimates. pERC noted that carfilzomib and Dex are likely to be used in second relapse, where effective treatment options after this are unlikely to lead to a substantially prolonged survival. Based on this, input from the CGP noted that the likelihood of living an additional 10 years in patients in second relapse and

having advanced disease are small. Furthermore, the data cited by the submitter to support the use of the 20-year time horizon were not representative of the ENDEAVOR trial population and were considered to be inappropriate to support long-term efficacy data for the ENDEAVOR trial population. Overall, pERC supported the use of a 10-year time horizon by the EGP. pERC also acknowledged the absence of randomized trials to demonstrate similar efficacy between the two dosing regimens of bortezomib specifically in the patient population under consideration. pERC however noted that clinical practice has shifted toward the use of once-weekly dosing of bortezomib, as discussed further in the Evidence In Brief section of the pERC final recommendation, based on comparative trials conducted in other indications for patients with multiple myeloma. pERC recognized that consensus among the clinical community supports the use of once-weekly bortezomib in multiple myeloma and agreed with the CGP that the appropriate comparator for carfilzomib plus Dex would be a bortezomib-containing regimen that employs the once-weekly dosing of bortezomib.

pERC discussed the feasibility of implementing a funding recommendation for carfilzomib plus Dex. pERC agreed that the carfilzomib-based triplet therapy (recently recommended for reimbursement by pERC) and the carfilzomib plus Dex regimen would not be used sequentially as there would not be a scenario where patients would be eligible for both. Therefore, carfilzomib plus Dex is expected to be an alternative therapy used in instances where patients are not eligible for the triplet therapy. However, pERC agreed that the optimal sequencing of carfilzomib plus Dex and other available or potentially soon to be available treatments for multiple myeloma is currently unknown. pERC recognized that provinces would need to address this issue upon implementation of carfilzomib funding. Collaboration among provinces to develop a common approach would be of value. pERC also agreed that patients eligible for carfilzomib plus Dex should be given a dose based on the ENDEAVOR trial protocol. pERC noted that the administration of carfilzomib is resource intensive. Therefore, 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 financial and human resources. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the Provincial Advisory Group related to the definition of disease progression in this setting. pERC agreed that standard definitions for disease progression as outlined in the International Myeloma Working Group (IMWG) Uniform Response Criteria should be used, as was done in the ENDEAVOR trial.

Factors that most influenced the budget impact analysis included treatment duration, treatment pathway for patients who are ineligible for transplant, number of eligible patients, and market uptake. Overall, pERC agreed that carfilzomib may have a substantial budget impact because of a number of factors, including the high cost of the drug, the potentially large patient population, and the unknown duration of treatment, as treatment is continued until disease progression or unacceptable toxicity.

EVIDENCE IN BRIEF

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

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Input from one patient advocacy group (Myeloma Canada)
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group (Myeloma Canada)
- One clinician group (Myeloma Canada Research Network [MRCN])
- PAG
- The submitter (Amgen Canada Inc.).

The pERC Initial Recommendation was to recommend reimbursement of carfilzomib (Kyprolis) in combination with dexamethasone (Dex) for patients with relapsed multiple myeloma with a good performance status who have received one to three prior treatments, on the condition that the cost-effectiveness be improved to an acceptable level. Feedback on the pERC Initial Recommendation indicated that the patient advocacy group, registered clinician group, and PAG agreed with the Initial Recommendation while the manufacturer agreed in part with the Initial Recommendation. Although all stakeholders supported conversion to a Final Recommendation, the manufacturer added a sufficient number of requests for changes to the Guidance Reports and pERC initial recommendation, that pERC was obliged to consider them before making a Final Recommendation.

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of carfilzomib plus dexamethasone (Dex) in the treatment of patients with relapsed multiple myeloma following one to three prior treatments.

Studies included: Randomized controlled trial

The pCODR systematic review included one open-label randomized controlled trial, ENDEAVOR, which randomized 929 patients with relapsed or refractory multiple myeloma to receive carfilzomib plus Dex (n = 464) or bortezomib plus Dex (n = 465). Treatments were given until disease progression, withdrawal of consent, or occurrence of unacceptable toxic effects. Key inclusion criteria required that patients have a creatinine clearance (CrCL) ≥ 15 mL/min and ≥ six-month proteasome inhibitor treatment-free interval before enrolment.

The pCODR review also provided contextual information on the ASPIRE and ENDEAVOR trials. A summary of key similarities or differences between the inclusion criteria, baseline characteristics, and results was presented for the two trials. pERC agreed that the most notable difference between the two trials was related to the inclusion criteria regarding renal function. While ASPIRE had a more stringent cut-off of CrCL ≥ 50 mL/min, ENDEAVOR enrolled patients with CrCL ≥ 15 mL/min. Other observed differences include numerically more patients in ENDEAVOR having International Staging System (ISS) stages I and II-III disease, high cytogenetics risk, and history of peripheral neuropathy, and having received prior treatment with an immunomodulatory agent (lenalidomide and thalidomide). More patients in ENDEAVOR were Eastern Cooperative Oncology Group (ECOG) 0 and fewer patients received three prior lines of treatment, including bortezomib. Observed progression-free survival (PFS) in ENDEAVOR was much shorter than that in ASPIRE study (intervention versus comparator: 18.7 versus 9.4 in ENDEAVOR and 26.3 versus 17.6 in ASPIRE, respectively), although the absolute magnitude of difference was the same between the two studies (9.3 months) and the hazard ratios (HRs) in the two studies were similar. pERC agreed that caution is needed in interpreting these differences, as it is unknown whether the observed differences in the magnitude of PFS between the two studies were caused by or related to the differences of the baseline characteristics of patients included in the two studies. Additionally, there could also be bias due to differences in unknown confounding variables.

Patient populations: Majority previously treated with bortezomib

Baseline characteristics were well balanced between treatment groups. The median age of patients in the ENDEAVOR study was 65.0 years and 15% of patients were older than 75 years. The majority of patients in the study had an ECOG performance status (PS) of 0 (49.0%) or 1 (44.5%), while 30 (6.5%) of patients had an ECOG PS of 2. Patients had received a median of two previous therapies and 57.3% and 58.5% of patients in the carfilzomib and bortezomib groups had prior transplant, respectively. Bortezomib was used previously by 54% of patients in both groups. However, the number of patients who were refractory to prior bortezomib treatment was low (3.2% and 4.1%) in the carfilzomib and bortezomib groups, respectively. Other prior therapies included lenalidomide (38% in both groups) and thalidomide (45% and 53% in the carfilzomib and bortezomib groups, respectively), while less than 1% of patients in both groups had previously received carfilzomib. Patients previously treated with carfilzomib or bortezomib were permitted entry into the trial provided they had achieved at least a partial response before relapse or progression, were not discontinued due to toxic effects, and had had at least a six-month proteasome inhibitor treatment-free interval before enrolment.

Carfilzomib was dosed in a step-wise manner (20 mg/m² on days 1 and 2 of cycle 1; 56 mg/m² given thereafter; 30-minute intravenous [IV] infusion) on days 1, 2, 8, 9, 15, and 16 and Dex (20 mg oral or IV) on days 1, 2, 8, 9, 15, 16, 22, and 23 of a 28-day cycle. Bortezomib was dosed as a 1.3 mg/m², three- to five-second IV bolus or subcutaneous (SC) injection on days 1, 4, 8, and 11, and Dex (20 mg oral or IV infusion) on days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle. pERC considered the dose of carfilzomib used in the ENDEAVOR trial to be different from that used in the ASPIRE trial (20 mg/m^2 starting dose followed by 27 mg/m^2 thereafter). Given that there is no clinical evidence to confirm or refute similar efficacy between the two doses, pERC agreed that patients eligible for the carfilzomib plus Dex doublet should be given a dose based on the ENDEAVOR trial protocol. pERC acknowledged that an ongoing trial, S1304, investigating high versus to low dose carfilzomib plus Dex in patients with relapsed or refractory multiple myeloma, may provide evidence to address such a question. The committee acknowledged that information was not available on the trial to determine whether or not the comparison being made between doses included the 56 mg/m² versus 27 mg/m² doses used in the ASPIRE and ENDEAVOR trials. The estimated primary completion date for this trial is February 2018. The majority of patients (~80%) in the bortezomib plus Dex group also received bortezomib SC as the sole route of administration, while 19.7% of patients received bortezomib IV exclusively. pERC agreed that the SC and IV route of administration of bortezomib have been demonstrated to have noninferior efficacy in a randomized controlled trial; however, the SC route is associated with reduced toxicity. Therefore, it is anticipated that patients will predominantly receive bortezomib as an SC administration.

Key efficacy results: Progression-free survival and overall response rate benefit; trend in overall survival benefit

The key efficacy outcome deliberated upon by pERC was PFS, the primary outcome of the ENDEAVOR trial. pERC noted that there was a statistically significant and clinically meaningful improvement in PFS reported in favour of the carfilzomib plus Dex group with an absolute magnitude of benefit in PFS of 9.3 months [HR of 0.53 (CI, 0.44 to 0.65; $P < 0.0001$)]. Median PFS was 18.7 versus 9.4 months in the carfilzomib and bortezomib groups, respectively (HR = 0.53; 95% CI, 0.44 to 0.65; $P < 0.0001$). pERC noted that efficacy outcomes were consistent across most of the assessed subgroups. Of note, pERC could not comment on the efficacy and safety of carfilzomib plus Dex in patients who were previously refractory to bortezomib treatment. Having considered the limitations associated with drawing a conclusion based on a small subgroup of patients (3.2% and 4.1% in the carfilzomib plus Dex and bortezomib plus Dex groups, respectively), the Committee agreed that clear evidence would be needed to determine whether or not the use of a newer proteasome inhibitor in patients refractory to bortezomib would be reasonable.

Overall survival (OS) was a secondary end point in the trial. At the time of the latest analysis, median OS had not been reached in either arm. At the 3 year updated analysis, a trend was noted favouring carfilzomib plus Dex (HR 0.805; 95% CI, 0.646 to 1.003, one-sided $P = 0.0263$) as it did not cross the pre-specified boundary for statistical significance. Overall response rate (ORR) was 77% versus 63% [2.03 (1.52 to 2.72); $P < 0.0001$] in the carfilzomib plus Dex compared with bortezomib plus Dex groups, respectively. pERC agreed that the proportion of patients achieving objective response, including complete (13% and 6%) and very good partial response (54% and 29%) in the carfilzomib plus Dex and bortezomib plus Dex groups, respectively; was meaningful, as depth of response in myeloma may be an indicator for OS benefit.

Patient-reported outcomes: Maintenance of quality of life

Patient-reported outcomes were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core Module (QLQ-C30), the Multiple Myeloma Module (QLQ-MY20), and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (subscale questionnaire) (FACT/GOG–Ntx). Patients treated with carfilzomib plus Dex had, on average, better global health status and/or quality of life (QoL) compared with patients treated with bortezomib plus Dex (between-group difference: 3.51; 95% CI, 1.97 to 5.06); however, the minimal important difference (MID, 5 points) was not met. Similar treatment differences were observed on the QLQ-C30 Fatigue, Pain, and QLQ-MY20 Side Effects of Treatment subscales; however, the MIDs were not reached. No treatment differences were observed between carfilzomib and bortezomib for the subscales of nausea/vomiting, Physical Functioning, Role Functioning, and Disease Symptoms. Using the FACT/GOG–Ntx scale, on average better scores were reported; however, MIDs have not been established for this scale. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer related to additional results on the patient-reported outcomes provided within the feedback. pERC noted that the information in the manufacturer's feedback suggested that MIDs were met at two time points for global health status and were approached at two other measurement points. A review of the feedback by the Methods team indicated that these data were not available during the review, as only limited data were available on patient-reported outcomes. Given the limited information available on patient-reported outcomes, lack of any statistical analysis to support that differences may exist, and exploratory nature of patient-reported outcomes in the trial, pERC agreed that caution should be used in interpreting the results within the feedback document.

pERC noted that maintenance and/or improvements in QoL are important patient values. Although improvements were not reported, carfilzomib appears to have at least maintained patients' QoL. pERC agreed that this was a meaningful outcome for patients.

Safety: Greater frequency of grade 3 or higher toxicities with carfilzomib

pERC discussed the toxicity profile of carfilzomib plus Dex and noted that a greater proportion of patients in the carfilzomib plus Dex group experience grade 3 or higher adverse events (339 [73.2] versus 305 [66.9]) and grade 3 or higher serious adverse events [93 (20%) and 67(15%)] compared with the bortezomib plus Dex group, respectively. Among key adverse events of interest, most were higher in the carfilzomib plus Dex group except for grade 3 or higher peripheral neuropathy, which occurred more frequently in the bortezomib plus Dex group (8.3% vs. 2.2%). In a post-hoc analysis among patients aged ≥ 75 years, all grades cardiac failure was increased in patients in the carfilzomib compared to the bortezomib group. A total of 153 (33.0%) patients in the carfilzomib and 171 (36.8%) in the bortezomib group died. Deaths due to an adverse event during treatment or within 30 days of receiving the last dose of study treatment was reported in 6.0% and 4.5% of patients in the carfilzomib pus Dex and bortezomib plus Dex group, respectively. Most deaths were attributed to adverse events (5.0% versus 3.4%, respectively). Deaths due to adverse events after 30 days of the last dose were 1.5% in the carfilzomib arm and 0.9% in the bortezomib arms.

pERC agreed that the toxicity profile of carfilzomib plus Dex is higher than that observed in the bortezomib plus Dex group. Given that the majority of patients who will be eligible for carfilzomib plus Dex are older and had transitioned through multiple lines of treatment, an increase in grade 3 adverse events and grade 3 serious events is not insignificant. However, pERC agreed with the Clinical Guidance Panel (CGP) that these adverse events are manageable.

Need and burden of illness: Patients ineligible for carfilzomib plus lenalidomide plus dexamethasone therapy

In 2016, 2,700 patients were diagnosed with myeloma, and 1,450 patients died of the disease. Despite significant advancements in the treatment and life expectancy of patients with multiple myeloma, it still remains an incurable disease and patients will relapse following initial therapy. The five-year survival for all patients is 48.5%. While bortezomib- or lenalidomide-based therapies are currently the standard treatment options in the second-line setting, superiority of one regimen over the other has not been conclusively demonstrated. Given that both options in the second-line setting have demonstrated an OS benefit, the choice of therapy largely depends on regimens used in the first line. In the first-line setting, younger patients (i.e., < 70 years) may also be eligible for bortezomib-based induction followed by autologous stem cell transplant (ASCT) and maintenance low-dose lenalidomide. pERC noted that younger patients may be eligible for a second transplant if they attain a prolonged remission with their first

transplant; however, given that most myeloma patients are older, receiving a second transplant is not usually an option. Recently, carfilzomib in combination with lenalidomide and Dex was approved for reimbursement in the relapsed setting based on an improvement in PFS and a trend toward improvements in OS. pERC noted that all patients may not be eligible for the triplet therapy, as eligibility will depend on patients' age, prior treatment history, renal function, and other relevant considerations (e.g., comorbidities). pERC therefore agreed that novel therapies that further improve survival are a continued need for these patients.

Registered clinician input: Progression-free survival benefit and durable response rates with carfilzomib plus dexamethasone

Clinicians providing input identified that current treatments for relapsed/refractory multiple myeloma include lenalidomide, bortezomib, cyclophosphamide, melphalan, and pomalidomide, while ASCT could be considered for eligible patients. Clinicians providing input noted that depending on the treatment history of patients, between 10% and 75% of patients could be eligible to receive carfilzomib as per the currently requested reimbursement indication. They agreed that carfilzomib plus Dex is superior to bortezomib plus Dex, as it has demonstrated improvement in PFS and very deep and durable response rates. Clinicians acknowledged that toxicities were increased with carfilzomib; however they were manageable. The minimal risk of peripheral neuropathy was also considered to be a benefit.

Related to sequencing of treatment, clinicians indicated that the following patients would be good candidates for carfilzomib plus Dex treatment: Patients who have received ASCT and relapsed on lenalidomide maintenance at first or second relapse; relapsed patients with high-risk cytogenetics; elderly patients who have previously been treated with bortezomib plus melphalan plus prednisone or, as a variation, cyclophosphamide plus bortezomib plus Dex (CyBorD) for nine cycles and subsequently received second-line therapy consisting of lenalidomide plus Dex. Clinicians stated that carfilzomib should not be used in patients with active cardiac problems or with cardiac insufficiency or in patients refractory to bortezomib. Clinicians also acknowledged that the treatment landscape in multiple myeloma is rapidly changing and it is anticipated that the treatment algorithm will change over time, while some patients will be treated in clinical trials. pERC acknowledged input from registered clinicians and concluded that carfilzomib plus Dex would be a reasonable treatment option for patients ineligible for the triplet therapy with carfilzomib plus lenalidomide plus Dex. This includes, but is not limited to, patients who have previously been treated with a lenalidomide-containing regimen and who no longer meet the eligibility criteria for the triplet therapy, and patients who are not eligible for the triplet therapy due to age or pre-existing conditions (e.g., impaired renal function)

PATIENT-BASED VALUES

Values of patients with multiple myeloma: Disease and treatment-related symptom control

Patients described infections as the most important aspect of myeloma to control, followed by kidney problems, pain, mobility, neuropathy, fatigue, and shortness of breath. For patients, their ability to work was most affected by symptoms associated with their disease, followed by ability to exercise, travel, volunteer, conduct household chores, fulfill family obligations, and spend time with family. Among 295 patients, more than 70% had received Dex, bortezomib, and/or lenalidomide in prior therapies. Sixty per cent had also had ASCT. Patients indicated that side effects of prior treatments included fatigue (88%), neuropathy (62%), insomnia (57%), stomach issues (48%), nausea (46%), shortness of breath (43%), pain (38%), and confusion (30%).

Among 202 patients, financial challenges associated with treatment included drug and parking costs (51% each), travel costs (33%), and loss of income due to work absence (32%). Twenty-five per cent of patients indicated they had no financial hardship. Among 155 patients, 74% indicated they had no hardships in accessing treatment while 23% experienced hardships. Among caregivers who had a family member treated with carfilzomib, challenges encountered because of treatment included side effects due to treatment and reduction in QoL. Caregivers, however, felt that carfilzomib was the best treatment for their family member.

Patient values on treatment: Quality of life, choice of treatment, minimize side effects

A total of 344 patients provided input. Among 261 patients providing input, 36% indicated that maintaining QoL was important when treating their myeloma followed by managing and/or minimizing side effects (20%), controlling disease (19%), having access to effective treatments (15%), controlling symptoms (13%),

achieving or maintaining remission, and prolonging survival (7% each). Among 294 patients, 97% said that it is very important to access effective treatment options for their myeloma, 86% said it was very important for them and their physician to have choice based on each drug's known side effects, and 89% indicated that improvements in QoL was a very important consideration for new treatment options. Among 253 patients, 8% indicated a willingness to tolerate treatment-related side effect while 7% were not.

Among 10 patients with experience using carfilzomib in combination with Dex, shortness of breath, diarrhea, fatigue, nausea, pneumonia, anemia, fever, thrombocytopenia, and neutropenia were the least tolerable side effects. On a scale of 1 to 5 (1 being "many more side effects," and 5 being "far fewer side effects"), 70% of patients rated carfilzomib as a 3 or higher. On a similar scale (1: "poor quality of life"; 5: "excellent quality of life"), 90% of patients rated their QoL as being 3 or higher and 20% as 4 or higher. The convenience of taking carfilzomib was rated as being 3 by 50% of patients (1: "not at all convenient"; 5: "extremely convenient"). pERC discussed the interpretation of patient input as related to the convenience of administration and compared it with input from the pCODR PAG, which indicated that carfilzomib is associated with an intense dosing schedule and the need for an intense hydration protocol. pERC noted that patients' input about the convenience of therapy was based on responses to a question that queried the broad experience of taking carfilzomib (the convenience of taking carfilzomib with respect to day-to-day activities and immediate or intolerable side effects related to treatment) as opposed specific queries about the impact of an intense dosing schedule and intense hydration protocol. pERC also acknowledged that numerical values from the patient input are not intended to capture data akin to clinical trial evidence.

Four out of eight patients indicated that carfilzomib plus Dex met their expectations of treatment. Among eight of these patients, disease control (50%) and remission (38%) were rated as important expectations for treatment. Among 39 patients with experience using carfilzomib in combination with Dex and other treatments, 41% indicated it to be extremely effective, while 10% said it was not effective. Compared with other therapies, 25% considered carfilzomib to be far more effective, while 10% felt it was not as effective. Carfilzomib was very tolerable for 31% of patients and completely intolerable for 5%. According to these patients, the least tolerable side effects associated with carfilzomib were fatigue, shortness of breath, diarrhea, anemia, neutropenia, nausea, fever, thrombocytopenia, and pneumonia.

pERC noted that the results of the ENDEAVOR trial demonstrated that carfilzomib plus Dex provides improvements in PFS and at least maintenance of QoL. Carfilzomib plus Dex also provides patients with an effective treatment option. pERC, however, noted that grade 3 or higher adverse events and serious adverse events were more frequent in the carfilzomib group. pERC agreed that these side effects were manageable, but nonetheless, they were not insignificant. Overall, pERC agreed that carfilzomib plus Dex aligned with patient values.

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 Dex with bortezomib plus Dex for the treatment of patients with relapsed multiple myeloma who have received one to three prior therapies.

Basis of the economic model: Clinical and cost inputs

Costs considered in the analysis include drug acquisition costs, subsequent treatment costs, drug administration and monitoring costs, adverse event management costs, and palliative care costs.

The clinical effects considered in the analysis were based on OS and PFS estimates from the ENDEAVOR trial and extrapolation beyond the trial period. In addition, other clinical effects estimates considered include time to treatment discontinuation, adverse events, and adverse events due to subsequent treatments.

Drug costs: Carfilzomib dose higher, treatment until progression, high drug cost

At the list price, carfilzomib costs $1,533.33 per single-use vial of 60 mg. Carfilzomib is administered as an IV dose on two consecutive days, each week for three weeks (days 1, 2, 8, 9, 15, 16) followed by a 12-day rest period (days 17 to 28).

- For the starting dose of 20 mg/m^2 in cycle 1 on days 1 and 2, followed by an increase to 56 mg/m^2 (if tolerated) on days 8, 9, 15, and 16, carfilzomib cost $409.53 per day and $11,466.84 per 28-day course. When wastage is considered, carfilzomib costs $547.50 per day and $15,330.00 per 28-day cycle.
- For all subsequent cycles, carfilzomib at the dose of 56 mg/m^2 (days 1, 2, 8, 9, 15, and 16) costs $521.22 per day and $14,594.16 per 28-day course. When wastage is considered, carfilzomib costs $657.00 per day and $18,396.00 per 28-day cycle.

Based on a generic list price, bortezomib costs 1,402.4200 per 3.5 mg vial. At a recommended dose of 1.3 mg/m^2 on days 1, 4, 8, 11 of each 21-day cycle, bortezomib costs:

- $168.67 per day and $4,722.82 per 28-day course.

Dex costs 0.3046 per 4 mg tablet. When combined with bortezomib and at the recommended dose of 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 of a 28-day cycle, Dex costs:

- $0.5802 per day and $16.2456 per 28-day course.

When combined with carfilzomib and at the recommended dose of 20 mg oral or IV infusion on days 1, 2, 8, 9, 15, 16, 22, 23 of a 28-day cycle, dexamethasone costs:

- $0.4351 per day
- $12.18 per 28-day course

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 60 mg vial size was available. pERC therefore supported the EGP's use of the 60 mg package and wastage associated with this vial, given this is the vial currently available to jurisdictions. However, pERC acknowledged that the incorporation of wastage into the analysis had a minimal impact on the incremental cost-effectiveness ratio (ICER)

Cost-effectiveness estimates: Time horizon

pERC deliberated upon the cost-effectiveness of carfilzomib plus Dex compared with bortezomib plus Dex, based on the submitted economic evaluation and reanalysis estimates provided by the EGP. pERC noted that CyBorD may be used more often in Canadian clinical practice; however, the Committee acknowledged CGP input that indicated that a bortezomib-containing regimen, including bortezomib plus Dex, would be considered appropriate in the Canadian setting. pERC considered uncertainties in model inputs addressed by the EGP and agreed that the model time horizon had the largest impact on the ICER. pERC accepted the CGP input and highlighted the improbability of expecting a 20-year time horizon in patients with relapsed multiple myeloma who have a median age of 70 years, most of whom will have gone through several lines of treatment. pERC therefore accepted the EGP's use of a 10-year time horizon. In addition, the EGP's use of utilities from the trial (rather than utilities from the literature which are adjusted based on the trial data) and the modelling of once-weekly bortezomib dosing substantially affected the ICER. pERC noted concern expressed by the CGP indicating that the utility values used for the base case (adjusted literature values) were higher than what is typically expected in this patient population, and agreed that utilities collected from the trial would better represent the trial population. In addition, the CGP confirmed that bortezomib is dosed once per week in clinical practice compared with twice-weekly dosing. pERC considered the clinical rationale for both of these inputs and accepted the changes made by the EGP. The EGP's reanalyses estimates also included modifications to time spent on subsequent treatments and the method for extrapolating the OS data. pERC noted these two parameters had less of an impact on the ICER. Overall, pERC considered both the submitted base-case results ($192,997/QALY) and the EGP's range of reanalysis estimates ($261,648/QALY to $294,931/QALY) to be not cost-effective.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer criticizing the use of a 10-year time horizon and once-weekly dosing of bortezomib in the EGP's reanalyses estimates. pERC agreed with input from the CGP that carfilzomib and Dex is likely to be used in second relapse, where effective treatment options after this are unlikely to lead to substantially prolonged survival. At this stage of advanced disease the likelihood of living an additional 10 years is small in patients in second relapse (after receiving lenalidomide and bortezomib therapy) and having advanced disease. pERC also agreed with the CGP's conclusion that the sources of data provided by the submitter to support the use of a 20-year time horizon were not representative of the ENDEAVOR trial population. Therefore, survival data from these sources cannot be used to support long-term efficacy data for patients who are expected to be treated with carfilzomib plus Dex. pERC also noted feedback from the submitter indicating that the SEER data used to model long-term OS data were match adjusted using key variables to the ENDEAVOR trial population. Given the absence of information to determine whether or not the matching accounted for

patients with smoldering myeloma, pERC agreed that uncertainty remained in the use of the SEER registry data. pERC however acknowledged that the EGP's use of an alternative method to model long-term survival (Weibull curve for the full trial period) did not have a substantial impact on the ICER. pERC further acknowledged the absence of randomized trials to demonstrate similar efficacy between the two dosing regimens of bortezomib specifically in the patient population under consideration. pERC however noted that comparative trials have been conducted in other indications for patients with multiple myeloma and this evidence has demonstrated similar efficacy and lower toxicity in favour of the once-weekly dosing. Based on this, clinical practice has since shifted toward the use of once-weekly dosing of bortezomib. Although acknowledging the gap in evidence specifically in the indication under review, pERC recognized that consensus among the clinical community supports the use of once-weekly bortezomib in multiple myeloma. In the absence of evidence to switch back to twice-weekly dosing, pERC agreed with the CGP that the appropriate comparator for carfilzomib plus Dex would be a bortezomib-containing regimen that employs the once-weekly dosing of bortezomib.

pERC considered the EGP's comments on the flexibility of the model structure in allowing for the alteration of a number of parameters. pERC echoed the EGP's comments and commended the manufacturer in providing information that aids the pCODR review team and, in turn, pERC to appropriately evaluate the submitted information.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Large budget impact, sequencing of upcoming and current therapies, eligibility criteria for treatment

pERC discussed the feasibility of implementing a funding recommendation for carfilzomib plus Dex. pERC agreed that patients will not be eligible for both the triplet and double carfilzomib-based combination therapies. Based on clinical opinion, it is anticipated that the triplet therapy with carfilzomib plus lenalidomide plus Dex will be the preferred treatment option in patients who are not eligible for the triplet therapy, notably patients who were previously treated with lenalidomide and no longer meet the eligibility criteria for the triplet therapy and patients who are not eligible for the triplet therapy due to pre-existing conditions. However, pERC agreed that the optimal sequencing of carfilzomib plus Dex and other soon to be available or available treatments for 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 agreed that patients eligible for carfilzomib plus Dex should be given a dose based on the ENDEAVOR trial protocol. 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, because of the resource-intensive nature of the dose preparation and frequent dosing schedule, all of which may require significant output of financial and human resources.

pERC noted that the bortezomib plus Dex regimen was not used in the submitted budget impact analysis (BIA). Given that the use of a bortezomib-based regimen is considered to be appropriate in this population, the Committee accepted the use of CyBorD as a comparator in the BIA. A sensitivity analysis was conducted to remove the cost of cyclophosphamide, and assuming all other parameters remain the same, demonstrated that results would not be much more different with bortezomib plus Dex.

Factors that most influenced the BIA include treatment duration, transplant-ineligible patient treatment pathway, number of eligible patients, and market uptake. pERC considered that the eligible patient population will likely be divided among those who will receive the double therapy with carfilzomib plus Dex and the triplet therapy with carfilzomib plus lenalidomide plus Dex. The Committee was, however, uncertain about the number of patients who would qualify for each treatment regimen. Overall, pERC agreed that carfilzomib may have a substantial budget impact because of a number of factors, including the high cost of the drug, the potentially large patient population, and the unknown duration of treatment, as treatment is continued until disease progression or unacceptable toxicity.

DRUG AND CONDITION INFORMATION

Drug Information	• Newer proteasome inhibitor • Single-use vial of 60 mg • Cycle 1: starting dose, 20 mg/m^2 on days 1 and 2; target dose, 56 mg/m^2 thereafter on days 8, 9, 15, and 16 • Cycle 2 and subsequent cycles: 56 mg/m^2 on days 1, 2, 8, 9, 15, and 16.
Cancer Treated	• Relapsed or refractory multiple myeloma
Burden of Illness	• 2,700 Canadians were diagnosed, and 1,450 patients died of this disease in 2016 • Despite significant advancement, remains an incurable disease
Current Standard Treatment	• Bortezomib-based regimen (bortezomib plus dexamethasone [Dex]; CyBorD: cyclophosphamide, bortezomib, and Dex) • Lenalidomide plus Dex
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

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

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

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

- Kelvin Chan and Scott Berry, who were not present for the meeting
- Valerie McDonald, who did not vote because of her role as a patient member alternate.

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

- Scott Berry, Craig Earle and Jo Nanson who were not present for the meeting

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 dexamethasone for multiple myeloma through their declarations, seven 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

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

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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