pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

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

pERC Final Recommendation
This 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: Pomalidomide (Pomalyst) **Submitted Funding Request:** In combination with low-dose dexamethasone for patients with multiple myeloma for whom both bortezomib and lenalidomide have failed and who have received at least two prior treatment regimens and have demonstrated disease progression on the last regimen	
Submitted By: Celgene Inc.	**Manufactured By:** Celgene Inc.
NOC Date: January 20, 2014	**Submission Date:** January 13, 2014
Initial Recommendation: May 30, 2014	**Final Recommendation:** July 31, 2014

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding pomalidomide (Pomalyst) in patients with relapsed and/or refractory multiple myeloma who have previously failed at least two treatments, including both bortezomib and lenalidomide, and demonstrated disease progression on the last treatment, conditional on the cost-effectiveness being improved to an acceptable level. Pomalidomide should also be an option in rare instances where bortezomib is contraindicated, or when patients are intolerant to it but, in all cases, patients should have failed lenalidomide. pERC made this recommendation because it was satisfied that there is a net clinical benefit of pomalidomide in this setting. However, at the submitted price and based on the Economic Guidance Panel's range of best estimates of the incremental cost-effectiveness ratio, pomalidomide could not be considered cost-effective compared with best supportive care.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-effectiveness
Given that pERC was satisfied that there is a net clinical benefit of pomalidomide in patients with relapsed and/or refractory multiple myeloma, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of pomalidomide to an acceptable level. pERC noted that jurisdictions need to consider the impact of dose adjustments on capsule burden since pomalidomide is flat priced per capsule and not per milligram.

SUMMARY OF pERC DELIBERATIONS

pERC discussed that multiple myeloma is an uncommon cancer. Patients are commonly treated with alkylating agents followed by bortezomib and/or lenalidomide in various combinations with steroids such as dexamethasone. However, patients eventually become refractory or intolerant to these treatments and, when this occurs, treatment options other than supportive care are limited. Therefore, pERC agreed with the pCODR Clinical Guidance Panel that there is a need for effective treatment options for patients with relapsed and/or refractory multiple myeloma who have progressed following treatment with bortezomib and lenalidomide.

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 randomized controlled trial, MM-003 (San Miguel 2013), that evaluated pomalidomide plus low-dose dexamethasone compared with high-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma that have received at least two previous consecutive cycles of bortezomib and lenalidomide and had failed these previous treatments. pERC noted that there was a statistically significant improvement in both overall survival (4.6 months, HR=0.74 95% CI 0.56 to 0.97) and progression-free survival (2.1 months, HR=0.48, 95%CI: 0.39 to 0.61) that favoured pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone. pERC discussed the magnitude of benefit in progression-free survival and noted that, although this was modest, it was considered clinically meaningful in this population of heavily pre-treated patients. In addition, pERC noted that a meaningful survival benefit occurred, despite cross-over being permitted in the trial, which often masks an overall survival benefit. Upon reconsideration of the initial recommendation, pERC considered feedback received from the Provincial Advisory Group regarding the performance status (PS) of patients to be included in the funding population. pERC noted that although the majority of patients in MM-003 had a PS of 0-1, there was a significant minority that had an ECOG PS of 2-3. Therefore, pERC agreed that, in alignment with the trial population, pomalidomide should be made available to patients with an ECOG PS ≤ 3. There were also differences in quality of life measures favouring the pomalidomide group, which included longer median times to worsening of fatigue and emotional functioning in the pomalidomide group, which were clinically meaningful and statistically significant. pERC discussed the toxicity profile of pomalidomide and noted that adverse events appeared similar between the pomalidomide plus low-dose dexamethasone group versus the high-dose dexamethasone group. However, grade 3 and 4 neutropenia was significantly higher in the pomalidomide group. pERC also considered that thromboembolic events were similar between the two groups and noted that all patients receiving pomalidomide were required to take thromboprophylaxis. pERC discussed that patients would have had similar risks of vascular thrombosis (e.g. stroke) when receiving prior therapy with lenalidomide and this risk appears to be manageable in clinical practice. pERC also noted that more second primary malignancies were observed in the pomalidomide group compared with the control group. pERC concluded that the secondary malignancies observed in the study may not be due to pomalidomide treatment; alternatively they may potentially be related to the prior lenalidomide treatment. Therefore, pERC was uncertain how to interpret these data, as patients had been previously exposed to long-term lenalidomide treatment and the association between long-term lenalidomide exposure and secondary malignancy is currently more clear. Therefore, pERC considered the overall adverse event profile to be manageable. After deliberating on all of these factors, pERC concluded that there is a net clinical benefit associated with pomalidomide.

pERC deliberated upon input from one patient advocacy group on pomalidomide. pERC noted that the majority of patients considered that pomalidomide compared favourably with other treatments for multiple myeloma; however, some patients reported negative experiences or adverse events while receiving pomalidomide. However, pERC considered that some of these events may have been associated with the disease and not the drug. When considering the MM-003 study, pERC noted that the frequency and type of adverse events were generally similar between the pomalidomide group and the control group. Patient input also indicated that patients valued improvements in quality of life and treatments with manageable toxicities. They also valued being able to choose among drugs with different side effect profiles. pERC discussed that the MM-003 study provided evidence that there were differences in quality

of life favouring pomalidomide and that adverse events of pomalidomide are manageable. Therefore, pERC considered that pomalidomide aligned with patient values.

pERC deliberated upon the cost-effectiveness of pomalidomide compared with best supportive care. pERC noted that the pCODR Economic Guidance Panel's estimates were less favourable than the manufacturer's estimates. This was primarily because the definition of best supportive care used by the Clinical Guidance Panel and applied to the economic analysis was considered more appropriate than the manufacturer's definition. In the absence of other treatment options, and in a heavily pre-treated population, the CGP considered high-dose dexamethasone to be the most relevant comparison while the manufacturer included a number of different and more costly treatments in the best supportive care arm that both the CGP and pERC would have expected to have been used earlier in treatment. The manufacturer's approach reduces the cost differential between pomalidomide and best supportive care. Upon reconsideration of the Initial Recommendation, pERC considered feedback received from the manufacturer regarding the appropriateness of the composite BSC arm used in the submitted economic evaluation as compared to the pCODR Economic Guidance Panel's use of high dose dexamethasone. pERC noted the rationale provided by the submitter and acknowledged that, in general, an economic comparator should reflect real life practice and not necessarily the clinical trial comparator. In this instance however, pERC acknowledged the pCODR Clinical Guidance Panel's position that indicated the absence of robust clinical evidence supporting the submitter's proposed comparators included in the composite BSC arm. pERC thus agreed that it would not be appropriate to include potential cost impacts of alternative treatments in a cost-effectiveness analysis without having knowledge of their potential impact on efficacy. As such, pERC further reiterated its agreement with the CGP and concluded that the EGP's use of high dose dexamethasone, in line with the clinical trial population, was appropriate. In addition, the manufacturer's estimates likely overestimate the post-progression survival benefit of pomalidomide. Therefore, pERC accepted the EGP's range of estimates and concluded that pomalidomide could not be considered cost-effective at the submitted price.

pERC discussed the feasibility of implementing a funding recommendation for pomalidomide. pERC noted that registration due to the controlled distribution of pomalidomide would likely not be a barrier as patients would already be registered in this program when they previously received treatment with lenalidomide. pERC acknowledged the Patient Advocacy Group's feedback reaffirming that registration to the controlled distribution program would not be a barrier to implementation; however, pERC noted that the addition of a new drug to this the program would require on-going pharmacy and human resources to manage the controlled distribution. pERC also discussed that these patients would previously have received prophylaxis and been monitored for thromboembolism while receiving lenalidomide. Therefore, the duration of this monitoring and these supportive care costs would be extended for patients going on to receive pomalidomide. pERC discussed the pCODR Clinical Guidance Panel's position that the benefit of pomalidomide likely extends to patients with slowly progressing disease, even though these patients were not included in the MM-003 study. However, during the deliberation on the initial recommendation, pERC considered that there was insufficient evidence to be able to make a recommendation to fund pomalidomide in this population and that the trial inclusion criteria should be followed when defining patients with multiple myeloma for pomalidomide eligibility. Upon reconsideration of the Initial Recommendation, pERC re-deliberated upon the pCODR Clinical Guidance Panel's position that the benefit of pomalidomide likely extends to patients with slowly progressing disease. pERC considered current clinical practice in multiple myeloma and noted that, in general, treating oncologists do not restrict treatment of patients based upon disease progression rate. pERC also noted that while the study may have been conducted to demonstrate efficacy in a rapidly progressing patient population, it would be reasonable to conclude that the benefit of the drug likely extends to a broader population. In addition, pERC considered current treatment options for patients with slowly progressing disease and discussed the variable availability of bortezomib for re-treatment in provinces in this setting. pERC noted that the availability of pomalidomide to this broader patient population would also provide a treatment option for patients who would otherwise have no other treatment option outside of BSC. pERC discussed the feasibility of implementing a funding recommendation for pomalidomide with the inclusion of patients with slowly progressing disease. pERC noted that provinces may have an additional budgetary impact due to the expansion of the funding population. pERC also noted that the manufacturer's estimates of cost-effectiveness followed the inclusion criteria of MM-003 and so the cost-effectiveness of pomalidomide in patients with slowly progressing disease is unknown. Therefore, pERC considered these additional uncertainties in the cost-effectiveness estimate and noted that provinces will need to manage these issues during implementation. pERC also noted that pomalidomide is priced per capsule and not per milligram, which is a barrier to implementation as it could lead to increased drug costs when dose adjustments are required and multiple tablet strengths are used.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient advocacy group (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 (Celgene Inc.)

The pERC initial recommendation was to fund pomalidomide (Pomalyst) in patients with relapsed and/or refractory multiple myeloma who had previously failed two treatments, including both bortezomib and lenalidomide, and who had demonstrated disease progression on the last treatment, conditional on the cost-effectiveness being improved to an acceptable level.

Feedback on the pERC Initial Recommendation indicated that the patient advocacy group and pCODR's Provincial Advisory Group agreed with the Initial Recommendation while the manufacturer agreed in part.

OVERALL CLINICAL BENEFIT

pCODR review scope

The objective of this review is to evaluate the effect of pomalidomide plus low-dose dexamethasone on patient outcomes, compared to standard treatments in patients with relapsed and/or refractory multiple myeloma for whom bortezomib and lenalidomide have failed and who have received at least two prior treatment regimens and have demonstrated disease progression on the last treatment regimen.

Studies included: one randomized controlled trial

The pCODR systematic review included one open-label randomized controlled trial (MM-003, San Miguel 2013) that evaluated the safety and efficacy of pomalidomide plus low-dose dexamethasone (n=302) compared to high-dose dexamethasone (n=153). In the trial, low dose dexamethasone consisted of 40 mg/day days 1, 8, 15 and 22 and high dose dexamethasone was 40 mg days 1-4, 9-12 and 17-20. The study was conducted in patients with relapsed and/or refractory multiple myeloma who had received at least two previous consecutive cycles of bortezomib and lenalidomide and who had failed the previous treatment with bortezomib or lenalidomide. Failure was defined as progressive disease on or before 60 days of treatment, progressive disease ≤ six months after achieving partial response, or intolerance to bortezomib. Intolerance to bortezomib was defined as development of treatment intolerance after a minimum of two cycles of bortezomib and had developed progressive disease on or before 60 days after completing their last treatment. Treatment was continued until progressive disease or unacceptable toxicity occurred. Patients were allowed to cross-over between the study arms following disease progression.

Patient population: heavily pre-treated population

The majority of patients in Study MM-003 had an ECOG performance status of 0 or 1 in both the pomalidomide plus low-dose dexamethasone group and the high dose dexamethasone group (82% and 80%, respectively). In both groups, approximately 94% of patients had failed more than two previous treatments, and the median number of previous treatments was five. In addition, a significant minority of patients included in the study had an ECOG PS of 2 or 3 (17% and 18%, respectively). In alignment with the trial patient population, pERC agreed that pomalidomide should be available to patients with and ECOG PS of ≤3. pERC also noted that there may be instances where a patient is rendered immobile due to bone metastasis and so considered to have an ECOG PS 3 while not necessarily having a high disease burden.

During the deliberation on the Initial Recommendation pERC discussed the pCODR Clinical Guidance Panel's position that the benefit of pomalidomide likely extends to patients with slowly progressing disease, even though these patients were not included in the MM-003 study. pERC discussed whether or not the results of study MM-003 in patients with rapidly-progressing disease could be generalized to patients with slowly-progressing disease. pERC noted that there is a small phase two study demonstrating that pomalidomide has an effect in all stages of disease; however, this evidence was not included in the pCODR systematic review and pERC did not consider it sufficient to make a recommendation in this population. Overall, during the deliberations on the Initial Recommendation, pERC considered there was insufficient evidence to be able to make a recommendation to fund pomalidomide in this population and that the inclusion criteria of Study MM-003 should be followed when defining patients with multiple myeloma for pomalidomide eligibility.

Upon reconsideration of the Initial Recommendation, pERC again discussed the Clinical Guidance Panel's conclusion that benefit of the drug likely extends to a broader population. pERC noted that while the MM-003 study may have been conducted to demonstrate efficacy in a high risk patient population, in general and based on current clinical practice, treating oncologists do not restrict therapy based on disease progression rate. In addition pERC considered current treatment options for patients with slowly progressing disease. pERC noted that some jurisdictions allow for bortezomib re-treatment in slowly progressing disease while others do not. Considering this variable availability of bortezomib re-treatment, pERC noted that in some jurisdictions, patients with slowly progressing disease would have no other treatment option outside of BSC. Based upon these discussions, pERC concluded that the eligibility criteria for pomalidomide treatment should be broadened to include slowly progressing disease.

pERC also considered feedback received from the Provincial Advisory Group regarding the potential use of pomalidomide in patients who would have received lenalidomide in the maintenance setting. pERC noted that this patient population would be treated with lenalidomide until disease progression and would be classified as relapsed or refractory upon progression. As such pERC agreed with the Clinical Guidance Panel's conclusion that patients who would have received lenalidomide in the maintenance setting meet the eligibility criteria for pomalidomide.

pERC also discussed that in addition to permitting pomalidomide in patients for whom bortezomib is contraindicated or who are intolerant to bortezomib, as per Study MM-003, pomalidomide should also be permitted when bortezomib cannot be administered to patients for logistical reasons. Upon reconsideration of the Initial Recommendation, pERC discussed feedback from the Provincial Advisory Group and further clarified instances in which bortezomib would not be feasible to administer logistically. pERC noted that these would be rare instances due to either geographic issues or restriction in access to care. pERC noted that these could be instances where patients may not have access to adequate nursing and appropriate expertise for bortezomib administration or where patients are located in remote areas and administration of injectable chemotherapy by an appropriately trained nurse is not feasible. In these rare instances, pERC agreed that bortezomib would be difficult to administer logistically and concluded that patients should be given the option to receive pomalidomide treatment. pERC noted that these logistic issues can occur with most/all intravenous therapies and are routinely addressed by the provinces through a number of mechanisms not unique to bortezomib. However, pERC confirmed that, as per Study MM-003, all patients receiving pomalidomide should have tried and failed lenalidomide.

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

Key efficacy outcomes deliberated on by pERC included progression free survival, the primary outcome of Study MM-003, and overall survival. pERC noted that there was a statistically significant improvement in both overall survival (12.7 vs 8.1 months, respectively; HR=0.74 95% CI 0.56-0.97) and progression-free survival (4.0 months vs 1.9 months, respectively; HR=0.48, 95%CI: 0.39 to 0.61) that favoured pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone. pERC discussed the magnitude of benefit in progression-free survival was modest but considered it to be clinically meaningful in this population of heavily pre-treated patients. In addition, pERC considered that this was accompanied by a meaningful overall survival benefit, despite cross-over being permitted between treatment groups upon disease progression, which tends to mask an overall survival benefit.

Quality of life: clinically and statistically significant improvements related to fatigue and emotional functioning

pERC discussed that there were also statistically significant improvements in two quality of life metrics favouring the pomalidomide group in Study MM-003: pomalidomide plus low-dose dexamethasone extended median times to meaningful worsening of fatigue (113 versus 60 days, p=0.04) and emotional functioning (190 versus 124 days, p=0.02) when compared to high-dose dexamethasone, as measured by the EORTC QLQ-30. pERC noted that no difference were measured for the other QOL domains. pERC did, however, consider that the magnitude of the differences in these two measures is clinically relevant and that these are important outcomes for patients who value improved quality of life, as noted in the patient advocacy group input.

Safety: thromboprophylaxis required but manageable adverse event profile

pERC deliberated upon the safety of pomalidomide based on the results of Study MM-003. pERC noted that more patients in the pomalidomide plus high-dose dexamethasone group reported grade 3 or grade 4 neutropenia compared to the low-dose dexamethasone group (48% versus 16%, respectively). However, other adverse events, including serious infections, appeared similar between groups. pERC noted that there was no difference in venous thromboembolic events between the two groups, despite a serious warning in the product monograph concerning deep vein thrombosis and pulmonary embolism. pERC discussed that in Study MM-003, all patients who received pomalidomide or who were at high risk of developing thrombosis were required to take thromboprophylaxis. Choice of prophylaxis treatment was at the discretion of the physician. pERC discussed that patients would have had similar risks of vascular thrombosis (e.g. stroke) when receiving lenalidomide earlier in their treatment course as this drug is in the same class as pomalidomide, and that this risk appears to be manageable in clinical practice. pERC also noted that more patients developed a second primary malignancy in the pomalidomide plus low-dose dexamethasone group compared with the high-dose dexamethasone group (4 versus 1, respectively) . However, pERC was uncertain about how to interpret these data as patients had been previously exposed to long-term lenalidomide, where the association between long-term use and secondary malignancy is now more established. pERC, therefore, concluded that the secondary malignancies observed in the study may not be due to pomalidomide treatment and were potentially related to the prior lenalidomide treatment as there was insufficient time on the drug. pERC also noted that, similar to lenalidomide, a controlled distribution programme was in place for pomalidomide. After deliberating on these factors, pERC considered that the overall toxicity of pomalidomide was acceptable and that the adverse event profile was manageable.

Need: effective treatment options for heavily pre-treated patients

pERC discussed that multiple myeloma is an uncommon cancer. It represents approximately 1.2% of all new cancers in Canada with an estimated 2500 Canadians being diagnosed in 2013 and 1350 dying from this disease. The median age at presentation is 70 years with a slightly higher incidence in males. The five year survival for all patients is 43%.

Patients with multiple myeloma are commonly treated with alkylating agents followed by bortezomib and/or lenalidomide in various combinations with steroids such as dexamethasone. However, patients eventually become refractory or intolerant to these treatments. Although steroid therapy alone is used for palliation and symptom control to slow progressive disease without negatively impacting quality of life, there is currently no clear standard of care for patients who are refractory or intolerant to these treatments. Therefore, pERC agreed with the pCODR Clinical Guidance Panel that there is a need for effective treatment options for patients with relapsed and/or refractory multiple myeloma who have failed treatment with both bortezomib and lenalidomide.

PATIENT-BASED VALUES

Values of patients with multiple myeloma: effective therapies with less fatigue and fewer infections

pERC deliberated upon input from one patient advocacy group on pomalidomide. Patients expressed the concern that their disease has a significant impact on their quality of life. Therefore, the majority of patients would value having access to effective treatments for myeloma. pERC discussed that the MM-003 study provided evidence that pomalidomide is an effective therapy that improves overall survival and

progression-free survival. pERC also discussed that, based on the results of the MM-003 study, pomalidomide provides patients with a longer period of time before fatigue and emotional functioning decline. Patients ranked infections as the most important myeloma-related complications to control. Infections were followed by kidney problems, pain, mobility, neuropathy, shortness of breath and fatigue. pERC noted that infections were similar between the pomalidomide and the control group in Study MM-003.

Patient values on treatment: better tolerated treatments and choice of side effects

pERC discussed that the majority of patients valued being able to choose among drugs with different side effect profiles. Patients expressed the importance of having a treatment alternative that is better suited for them. pERC acknowledged the large number of patients who provided input on their personal direct experiences with pomalidomide, which was very useful in determining if pomalidomide aligned with patient values. pERC also noted that the patient input provided a balanced perspective on the drug. For example, although the majority of patients considered that pomalidomide compared favourably with other treatments for multiple myeloma, some patients reported negative experiences with pomalidomide.

Fatigue was noted by most patients as the number one side effect of current treatments, followed by neuropathy, nausea and stomach issues. Although patients reported that adverse events occurred while receiving pomalidomide, pERC considered that some of these events overlapped with those associated with multiple myeloma and noted that it can be challenging when taking a drug to determine whether a given adverse event is associated with the drug or the disease. When considering the MM-003 study, pERC noted that the frequency and types of adverse events were generally similar between the pomalidomide group and the control group. pERC also noted that many of the adverse events associated with pomalidomide appear to be manageable. Therefore, pERC considered that pomalidomide aligned with patient values by providing an effective and tolerable treatment option for patients.

ECONOMIC EVALUATION

Economic model submitted: cost utility, differences in definition of best supportive care

The pCODR Economic Guidance Panel assessed a cost-effectiveness and cost-utility analysis of pomalidomide plus low dose dexamethasone versus best supportive care for patients with relapsed and/or refractory multiple myeloma. The patient population was defined similarly to those in the MM-003 study.

The submitter defined best supportive care as a combination of possible therapies (e.g., lenalidomide plus dexamethasone, bortezomib plus dexamethasone, stem cell transplantation, palliative care). However, the pCODR Clinical Guidance Panel considered that high-dose dexamethasone, as used in the MM-003 study, was the most appropriate form of best supportive care, or palliative care. Upon reconsideration of the Initial Recommendation, pERC considered feedback received from the manufacturer regarding the appropriateness of the composite BSC arm used in the submitted economic evaluation as compared to the Economic Guidance Panel's use of high dose dexamethasone. pERC discussed the evidence provided by the submitter and noted the absence of robust clinical evidence for the efficacy of these alternative options in the refractory setting. In general, pERC agreed that an economic comparator should reflect real life practice and not necessarily the clinical trial comparator. In this instance however, pERC noted the Clinical Guidance Panel definition of the appropriate comparator and agreed that there was no robust evidence of efficacy to support the submitter's proposed comparators in the composite BSC arm. pERC therefore agreed that it would not be appropriate to include potential cost impacts of alternative treatments into a cost-effectiveness analysis without having any knowledge of their potential impact on efficacy. As such, pERC further reiterated its agreement with the CGP and concluded that the EGP's use of high dose dexamethasone, in line with the clinical trial population, was appropriate.

Basis of the economic model: clinical and economic inputs

Costs considered in the analysis included treatment costs, the cost of treating adverse events, oncologist visits and transfusions.

The clinical effects considered in the analysis were based on estimates of overall survival and progression free survival from the MM-003 study. Quality of life estimates were obtained from both the trial and literature.

Drug costs: price per capsule rather than per milligram could increase drug costs

At the list price, pomalidomide costs $500.00 per 1 mg, 2 mg, 3 mg and 4 mg capsule. At the recommended dose of 4mg orally on days 1 to 21 of 28-day cycle, for a 70 kg patient, pomalidomide costs an average of $375.00 per day, distributed over a 28 day period, and $10,500.00 per 28 day course. pERC also discussed that pomalidomide is priced per capsule and not per milligram, which is a potential barrier to implementation because actual use in clinical practice could increase costs significantly. Although this is not expected to be common dosing practice, depending on the combination of capsules used to provide a 4 mg dose or the dose adjustments required to manage toxicity, the price of pomalidomide may be as high as $1500.00 per day and $42,000.00 per 28-day course.

Dexamethasone costs $0.3046 per 4 mg tablet.

- At the recommended dose of 40 mg on days 1, 8, 15 and 22 low-dose dexamethasone costs an average of $0.44 per day, distributed over a 28 day period, and $12.32 per 28-day course.
- At the recommended dose of 40 mg on days 1 to 4, days 9 to 12, and days 17 to 20, high-dose dexamethasone costs an average of $1.31 per day, distributed over a 28 day period, and $36.55 per 28-day course.

pERC also noted that in the MM-003 study, for all patients over 75 years, dexamethasone was given at 20 mg/day.

Cost-effectiveness estimates: costs of best supportive care and post-progression survival overestimated

pERC deliberated upon the cost-effectiveness of pomalidomide plus low-dose dexamethasone compared with best supportive care. pERC noted that the pCODR Economic Guidance Panel's estimates were less favourable than the manufacturer's. This was primarily because in the absence of other treatment options, and in a heavily pre-treated population, the CGP considered that high-dose dexamethasone would be the most relevant comparison. Therefore, pERC agreed that the definition of best supportive care used by the Clinical Guidance Panel was more appropriate than the manufacturer's. The manufacturer included a number of different and more costly treatments in the best supportive care arm that both the CGP and pERC would have expected to have used earlier in treatment, which led to an overestimate of the costs of best supportive care. The manufacturer's approach reduces the cost differential between pomalidomide and best supportive care. Upon reconsideration of the Initial Recommendation, pERC considered feedback received from the manufacturer regarding the appropriateness of the composite BSC arm used in the submitted economic evaluation as compared to the Economic Guidance Panel's use of high dose dexamethasone. As discussed above, pERC noted the absence of robust clinical evidence suggesting the superiority of alternative options over high dose dexamethasone and agreed with the Clinical Guidance Panel that high dose dexamethasone was the most appropriate comparator. In addition, the manufacturer's estimates likely overestimated the post-progression survival benefit of pomalidomide. It was noted that in the manufacturer's submitted model, the majority of the clinical benefit is a result of post-progression survival, which is unrealistic from a clinical perspective. The EGP's best estimates attempted to adjust for these factors; therefore, pERC accepted the EGP's range of estimates and concluded that pomalidomide could not be considered cost-effective at the submitted price. pERC further noted that the expansion of the treatment eligibility criteria to include patients with slowly progressing disease is likely to have an impact on the cost-effectiveness of pomalidomide. pERC acknowledged that the submitted economic analysis and EGP's reanalysis estimates were based on the MM-003 trial population which only included patients with rapidly progressing disease. pERC acknowledged this introduces additional uncertainty in the cost-effectiveness estimates and noted that provinces will need to manage these issues during implementation.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: flat pricing, additional resources

pERC deliberated upon the feasibility of implementing a funding recommendation for pomalidomide. pERC discussed input from PAG that identified the requirement for registration with the federally mandated monitoring program for pomalidomide. Although this might be a barrier that could delay access, pERC noted that most patients would already be registered in this program when they previously received treatment with lenalidomide. pERC acknowledged the Patient Advocacy Group's feedback confirming that registration to the controlled distribution program would not be a barrier to implementation; however, pERC noted that the addition of a new drug to this program would require on-going pharmacy and human resources to manage the controlled distribution.

pERC discussed input from PAG regarding the additional health care resources that would be required to monitor and treat toxicities associated with pomalidomide including neutropenia and venous thromboembolism. pERC noted that these patients would have previously received thromboprophylaxis and been monitored for thromboembolism while receiving previous lenalidomide therapy. Therefore, the duration of this monitoring and these supportive care costs would be extended for patients who go on to receive pomalidomide. pERC also noted input from PAG that indicated, although the number of eligible patients with multiple myeloma may be small, there would be a budget impact for a new line of therapy since palliative treatment with high-dose dexamethasone or cyclophosphamide/prednisone is relatively inexpensive. pERC further noted that the expansion of the treatment eligibility criteria to include patients with slowly progressing disease is likely to increase the number of eligible patients and have an additional budgetary impact on jurisdictions. pERC noted that provinces would need to consider this additional impact during implementation.

pERC also discussed that pomalidomide is priced per capsule and not per milligram, which is a potential barrier to implementation because actual use in clinical practice could increase costs significantly, depending on what combination of capsules is used.

DRUG AND CONDITION INFORMATION

Drug Information	• Immunomodulatory agent, thalidomide derivative • 1 mg, 2 mg, 3 mg and 4 mg capsule • 4 mg daily on day 1 to 21 in combination with low-dose dexamethasone 40 mg on days 1, 8, 15, and 22 of a 28-day cycle
Cancer Treated	• Relapsed and/or refractory multiple myeloma • After failure of both bortezomib and lenalidomide
Burden of Illness	• 1.2% of all new cancers in Canada • Five-year survival for all patients is 43%
Current Standard Treatment	• No clear standard of care after patients relapse on and/or become refractory to bortezomib and lenalidomide • Steroids alone used for palliative care and symptom control
Limitations of Current Therapy	• No effective treatment options at this stage of disease

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

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

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

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

- Dr. Chaim Bell, Dr. Scott Berry, Bryson Brown, Dr. Matthew Cheung and Dr. Paul Hoskins, who were not present for the meeting

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

- Dr. Chaim Bell, Dr. Scott Berry and Dr Maureen Trudeau who were not present for the meeting.
- Dr Matthew Cheung who was excluded from voting due to a conflict of interest.
- Carole McMahon who was excluded from voting due to her role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of pomalidomide (Pomalyst) for multiple myeloma, through their declarations, three members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

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