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

Drug: Lenalidomide (Revlimid) **Submitted Funding Request:** For the maintenance treatment of newly diagnosed multiple myeloma in patients after stem-cell transplantation	
Submitted By: Celgene Inc.	**Manufactured By:** Celgene Inc.
NOC Date: N/A	**Submission Date:** April 5, 2013
Initial Recommendation: October 3, 2013	**Final Recommendation:** October 22, 2013

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) recommends funding lenalidomide (Revlimid) as a maintenance treatment for patients with newly diagnosed multiple myeloma, following autologous stem-cell transplantation conditional on the cost-effectiveness being improved to an acceptable level. pERC made this recommendation because it was satisfied that there is a net clinical benefit of lenalidomide in this setting. However, at the submitted price and the Economic Guidance Panel's range of best estimates of the incremental cost effectiveness ratio, lenalidomide maintenance could not be considered cost-effective compared with placebo.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Price arrangements to improve cost effectiveness** Given that pERC was satisfied that there is a net clinical benefit to the use of lenalidomide maintenance therapy in patients with newly diagnosed multiple myeloma following ASCT, pERC noted that jurisdictions need to consider the cost impact of dose adjustments as lenalidomide has a relatively flat price per tablet rather than being priced per milligram. As such, actual use in clinical practice may significantly increase costs. **Additional Resources Required Due to Controlled Distribution** pERC noted that lenalidomide can only be obtained currently through a controlled distribution program and that expansion of lenalidomide use to the maintenance setting may require additional pharmacy and human resources to manage the controlled distribution.

SUMMARY OF pERC DELIBERATIONS

pERC discussed that for patients with newly diagnosed multiple myeloma, there is no standard therapy in the maintenance setting following autologous stem-cell transplantation (ASCT) and placebo is an acceptable comparator. However, it was noted that other potential maintenance treatments could include thalidomide and bortezomib but the role of these therapies in this setting is not clearly defined. Therefore, pERC agreed with the pCODR Clinical Guidance Panel that there is a need for effective treatment options in the maintenance setting.

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 two randomized double-blind placebo-controlled trials, IFM 2005-02 (Attal 2012) and CALGB 100104 (McCarthy 2012) that evaluated lenalidomide compared with placebo as a maintenance treatment in patients with newly diagnosed multiple myeloma, following treatment with autologous stem cell transplant (ASCT). pERC deliberated upon the results of these two studies and concluded that there is a net clinical benefit associated with lenalidomide. pERC noted that in both studies, there was a significant delay in disease progression (i.e., progression-free survival or time to progression) that favoured lenalidomide and that, in one of the studies, lenalidomide demonstrated a significant improvement in overall survival compared with placebo. pERC noted that quality of life was not measured in either of the studies but that the studies were, otherwise, well-designed. pERC also discussed the toxicity profile of lenalidomide and agreed with the pCODR Clinical Guidance Panel that toxicities were manageable. However, pERC noted that there were serious thromboembolic adverse events observed with lenalidomide. In addition, one of the trials was stopped because of an increased risk of second primary malignancies. Therefore, pERC recommends careful monitoring for these adverse events in patients receiving lenalidomide. pERC also noted that the duration of therapy with lenalidomide that would maximize clinical benefit while minimizing risks such as secondary malignancies is currently unknown and has not been evaluated in randomized controlled trials. Upon review of feedback from pCODR's Provincial Advisory Group on the appropriate stopping criteria for lenalidomide treatment, it was noted that this is an area that requires further study. pERC could not provide more guidance on the duration of lenalidomide treatment other than following the trial stopping criteria, which were disease progression and unacceptable toxicity.

pERC reviewed input from one patient advocacy group. pERC noted the large number of patients who had completed the patient survey and the large proportion of patients who had experience with lenalidomide. pERC considered that this provided high quality input that was very useful to pERC in determining if lenalidomide aligns with patient values. pERC noted that patients valued extending life and controlling disease, therefore the results of the IFM2005-02 and CALGB 100104 studies aligned with patient values. pERC also noted that patients who had experience with lenalidomide indicated that it was better tolerated than other treatment options. Therefore, pERC considered that lenalidomide aligns with patient values.

pERC deliberated upon the cost-effectiveness of lenalidomide maintenance compared with placebo. pERC noted that the pCODR Economic Guidance Panel's (EGP) estimates were less favourable than the manufacturer's but that both sets of estimates were considered high and not cost-effective at the submitted price. pERC concluded that the EGP's estimates were more realistic as they used a shorter and more reasonable time horizon and because the manufacturer's estimates likely overestimated the survival benefit of lenalidomide. pERC noted that the manufacturer's analysis used a longer time horizon of 40 years, compared with the EGP's analysis. Based on input from the pCODR Clinical Guidance Panel, the EGP used a time horizon of 15 years, which was considered more realistic. Upon review of feedback from the manufacturer on why they had used a 40 year time horizon, it was noted that the Committee considered a 15 year time horizon more appropriate based on input from the clinical panel and the uncertainty of extrapolating short-term trial data over a much longer period of time.

pERC discussed the feasibility of implementing a funding recommendation for lenalidomide. pERC noted that an initial dose escalation of lenalidomide is expected from 10 mg to 15 mg, as was observed in the clinical trials, but that doses would be expected to remain stable after this point. pERC also noted that because lenalidomide is priced per tablet, rather than per milligram, this could be a barrier to implementing lenalidomide as it could lead to increased drug costs when dose adjustments are required. pERC also noted that lenalidomide is only available through a controlled distribution program. Therefore, expanding lenalidomide access to the maintenance setting would require greater pharmacy resources and patient access may be limited in settings that do not have these additional resources.

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:

- pCODR's Provincial Advisory Group
- the Submitter (Celgene Inc.)

The pERC Initial Recommendation was to fund lenalidomide (Revlimid) as a maintenance treatment for patients with newly diagnosed multiple myeloma, following autologous stem-cell transplantation conditional on the cost-effectiveness being improved to an acceptable level. Feedback on the pERC Initial Recommendation indicated that both the Submitter and pCODR's Provincial Advisory Group agreed with the initial recommendation. The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the safety and efficacy of maintenance treatment with lenalidomide following autologous stem cell transplantation (ASCT), compared to an appropriate comparator, in patients with newly diagnosed multiple myeloma.

Studies included: two randomized controlled trials

The pCODR systematic review included two randomized, double-blind, placebo-controlled, phase 3 trials, IFM 2005-02 (Attal 2012) and CALGB 100104 (McCarthy 2012) that assessed the efficacy and safety of lenalidomide maintenance therapy compared to placebo maintenance in patients with newly diagnosed multiple myeloma following treatment with ASCT. Both studies randomized patients to lenalidomide maintenance (10 mg/day for the first 3 months, increased to 15 mg/day if tolerated, thereafter) or placebo maintenance

- For IFM 2005-02, the final efficacy analysis was conducted in July 2010. The study was unblinded but cross-over of placebo patients to lenalidomide was not permitted. Patients stopped receiving lenalidomide as of January 2011 due to safety concerns related to an increased incidence of second primary malignancies in patients receiving lenalidomide.
- For CALGB 100104, the study was terminated early (December 17, 2009, following a median follow-up of 18 months) due to the demonstration of statistically significant improvements in the primary efficacy outcome, time-to-progression, after a pre-planned interim analysis. Patients were then allowed to crossover to lenalidomide.

Upon review of feedback from pCODR's Provincial Advisory Group on the appropriate stopping criteria for lenalidomide, it was noted that pERC had previously indicated that the optimal duration of therapy with

lenalidmoide that would maximize benefit while minimize risk is unknown. pERC considered that this is an area that requires further study and that currently, pERC is unable to provide guidance on duration of therapy other than following the stopping criteria defined in the clinical trials. In both studies, lenalidomide was stopped upon disease progression or unacceptable toxicity.

The pCODR review also provided contextual information on two additional studies that assessed the benefit of lenalidomide maintenance in transplant-ineligible patients (Palumbo 2012) and the use of lenalidomide maintenance versus no maintenance in both transplanted and non-transplanted patients (Boccadoro 2013 and Cavallo 2013).

Patient populations:

The patient populations enrolled in the IFM 2005-02 and CALGB 100104 studies were similar and patient characteristics were generally balanced across treatment arms. Patients included in CALGB 100104 had an ECOG performance status of 0 or 1 and performance status was not specified in IFM 2005-02.

IFM 2005-02 included patients who had received 1 or 2 prior ASCTs (75% or 21%, respectively). Almost all patients had received prior consolidation treatment with lenalidomide 25 mg/day on days 1 to 21 of a 28-day cycle for 2 cycles following single or double ASCT.

The majority of patients in CALGB 100104 had received induction therapy with a regimen containing lenalidomide, thalidomide, or bortezomib, or a combination of the three. All patients in CALGB 100104 had received a single prior ASCT.

Key efficacy results: disease progression consistently controlled, overall survival benefit in one study

Key efficacy outcomes deliberated on by pERC included progression free survival (PFS) and time to progression (TTP), the primary outcomes for IFM 2005-02 and CALGB 100104 studies, respectively. pERC also deliberated on overall survival results from the two studies.

pERC noted that, in both studies lenalidomide demonstrated a statistically and clinically significant improvement in disease control as measured by progression free survival (PFS) or a similar endpoint, time to tumour progression (TTP). In IFM 2005-02 median PFS was 44 versus 24 months in the lenalidomide arm compared to the placebo arm, respectively (HR=0.50 95% CI: 0.41 to 0.64, P<0.001) as measured at the October 2011 cut-off. In CALGB 100104, statistically significant improvement in median time to progression was observed for lenalidomide compared to placebo, at the December 2009 and October 2011 pre-planned interim analysis and the January 2013 updated analysis, which had a median time to progression of 50 months versus 27 months in the lenalidomide compared to the placebo arm (HR= 0.51 95% CI: 0.39-0.66 P=NR).

pERC noted that lenalidomide demonstrated a statistically significant advantage in overall survival compared with placebo in the CALGB 100104 study (HR=0.61, 95%CI: 0.41 to 0.87, P=0.008, Jan 2013 analysis) but not the IFM 2005-02 study. pERC noted that quality of life was not measured in either of the studies. However, based on the improvements in progression-free survival, time to progression and overall survival, which favoured lenalidomide over placebo, pERC concluded that there is a clinical benefit associated with lenalidomide.

Safety: toxicity manageable but monitoring for second primary malignancies required

pERC also discussed the toxicity profile of lenalidomide based on the two studies. In the IFM 2005-02 study, a statistically significant higher rate of grade 3 or 4 thromboembolic events (6% versus 2%, respectively, P=0.01) and hematologic adverse events (58% versus 22%, P<0.001) were observed in the lenalidomide maintenance arm compared to the placebo maintenance arm. In the CALGB 100104 study, statistically significantly higher rates of grade 3 or 4 hematologic adverse events (59% versus 30%, P<0.001), neutropenia, anemia, and thrombocytopenia were observed in the lenalidomide maintenance arm than in the placebo arm. In addition, one of the trials was stopped because of an increased risk of second primary malignancies in patients receiving lenalidomide and in both studies, the incidence of secondary malignancies was higher in the lenalidomide arm than in the placebo arm (3.1 vs 1.2 per 100 patient-years; P=0.002, respectively, in IFM 2005-02 and 12.6% versus 6.6% patients, respectively, in the

CALGB 100104 study as of the January 2013 updated analysis). It was noted that based on the two trials, the pCODR Clinical Guidance Panel considered the second malignancy risk to be acceptable. pERC discussed these safety data and noted that careful monitoring of patients for toxicities was required for serious thromboembolic and hematologic adverse events and second primary malignancies.

Discontinuations due to adverse events were noted in both studies. In IFM 2005-02, more patients in the lenalidomide arm discontinued treatment due to adverse events compared to the placebo arm (27.1% versus 14.6%, respectively). In CALGB 100104, of the 143 patients who did not crossover to lenalidomide, 10.0% and 1.4% of patients discontinued therapy due to an adverse event in the lenalidomide and placebo arms, respectively. pERC noted that the optimal duration of therapy with lenalidomide that would maximize clinical benefit while minimizing risks such as second primary malignancies is currently unknown and has not been evaluated in randomized controlled trials or in any identified ongoing trials.

Considering these factors and the careful monitoring that was required, pERC agreed with the pCODR Clinical Guidance Panel that toxicities were manageable and expected based on previous experience with lenalidomide.

Need: effective treatments in maintenance setting

Myeloma is incurable in the vast majority of cases. It is expected that there will be 1,350 deaths from the disease in Canada in 2013. Autologous stem cell transplant is frequently performed as part of front line myeloma therapy. The pCODR Clinical Guidance Panel noted that this treatment is not curative but improving patient survival, remission duration and quality of life are important goals. pERC discussed that for patients with newly diagnosed multiple myeloma, there is no standard therapy in the maintenance setting and many patients do not receive maintenance treatment. Older chemotherapy regimens have not improved patient outcomes when used as maintenance therapy. It was noted that newer potential maintenance treatments include thalidomide and bortezomib; however, the role for these therapies in this setting is not clearly defined. Therefore, pERC agreed with the pCODR Clinical Guidance Panel that there is a need for effective treatment options in the maintenance setting.

PATIENT-BASED VALUES

Values of patients with multiple myeloma: extending life and controlling disease

pERC reviewed input from one patient advocacy group and noted the large number of patients who had completed a patient survey and that a large number of patients had experience with lenalidomide and had provided highly relevant input that was very useful to pERC in determining if lenalidomide aligns with patient values. Symptoms that patients considered important to control included infections, kidney problems, pain, loss of mobility, neuropathy, shortness of breath and fatigue. pERC also noted that patients valued extending life. Therefore the results of the IFM2005-02 and CALGB 100104 studies aligned with patient values.

Patient values on treatment: toxicities manageable and acceptable to patients

pERC noted that patients who had experience with lenalidomide indicated that it was better tolerated than other treatment options. While the addition of lenalidomide has some increased toxicity, patients considered that the degree of toxicity was manageable. In addition, patient input indicated that from a patient perspective, it is important to have a choice of treatments for their myeloma. Patient input indicated that side effects that are important to control or avoid with other possible treatment options included fatigue, neuropathy and stomach upset. Therefore, pERC considered that although lenalidomide has important toxicities that must be monitored, toxicities are acceptable to patients given the benefits of extending life and controlling disease. Therefore, lenalidomide aligns with patient values.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility

The pCODR Economic Guidance Panel assessed a cost-effectiveness and cost-utility analysis of lenalidomide compared to placebo for patients with multiple myeloma following chemotherapy and ASCT.

Basis of the economic model: clinical and economic inputs

Costs considered in the analysis included drug acquisition costs, laboratory monitoring costs, costs incurred following disease progression and costs of managing adverse events, including second primary malignancies.

Key clinical effects considered in the analysis were progression-free survival and overall survival estimates from the CALGB 100104 study (McCarthy 2012) and utilities from the literature.

Drug costs: higher drug costs if dose adjustments because lenalidomide priced per tablet

Lenalidomide has a relatively flat pricing structure that changes very little as dosage increases. The 5 mg, 10 mg, 15 mg tablets cost $340, $361 and $382, respectively. At the recommended dose of 10 to 15 mg per day, lenalidomide costs $361 to $382 per day and the average cost per 28-day cycle is between $10,108 and $10,696. pERC noted that because lenalidomide is priced per tablet, rather than per milligram, it could lead to increased drug costs when dose adjustments are required and multiple tablet strengths are used.

Cost-effectiveness estimates: influenced by overall survival and time horizon

pERC noted that the pCODR Economic Guidance Panel's (EGP) estimates were somewhat less favourable than the manufacturer's estimates of incremental cost-effectiveness for lenalidomide compared with placebo. pERC noted that the manufacturer's analysis used a longer time horizon of 40 years, compared with the EGP's analysis. Based on input from the pCODR Clinical Guidance Panel, the EGP used a time horizon of 15 years, which was considered more realistic. Upon review of feedback from the manufacturer on why they had used a 40 year time horizon, it was noted that the Committee considered a 15 year time horizon more appropriate based on input from the Clinical Guidance Panel and the uncertainty of extrapolating short-term trial data over a much longer period of time. In addition, the Clinical and Economic Guidance Panels considered that the survival advantage of lenalidomide in the period following disease progression may have been overestimated by the manufacturer as they were not supported by the clinical evidence. Although the manufacturer's analysis assumed an improvement in overall survival in favour of lenalidomide of a magnitude of slightly more than 4 years, based on input from the Clinical Guidance Panel, it is unclear that the true magnitude of overall survival benefit of lenalidomide is 4 years and it may be substantially less. The Panels also noted that the IFM 2005-02 study did not show a statistically significant overall survival improvement. Therefore, reanalyses by the EGP resulted in a smaller survival advantage for lenalidomide by assuming no survival advantage in the period following disease progression. pERC discussed that both the EGP's and the manufacturer's estimates of incremental cost-effectiveness were high and, therefore, lenalidomide, could not be considered cost-effective at the submitted list price. However, pERC considered that the EGP's estimates were more realistic because they used a shorter and more reasonable time horizon compared with the manufacturer and because the manufacturer's estimates likely overestimated the survival benefit of lenalidomide.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: pricing per tablet, monitoring toxicities and resources for controlled distribution program

pERC discussed input from pCODR's Provincial Advisory Group and the feasibility of implementing a funding recommendation for lenalidomide. pERC noted that an initial dose escalation of lenalidomide is expected from 10 mg to 15 mg, as was observed in the clinical trials, but that doses would be expected to remain stable after this point. pERC also noted that the relatively flat pricing structure of lenalidomide per tablet, rather than per milligram, would be a barrier to implementing lenalidomide as it could lead to increased drug costs when dose adjustments are required and multiple tablet strengths are used. pERC also noted that lenalidomide is only available through a controlled distribution program, as required by Health Canada. Therefore, expanding lenalidomide access to the maintenance setting would require greater pharmacy resources and patient access may be limited in settings that do not have these additional resources. pERC also noted that the increased risk of second primary malignancies and other serious toxicities observed with lenalidomide would require additional monitoring and health care resources.

DRUG AND CONDITION INFORMATION

Drug Information	• Immunomodulator, thalidomide analog • 5mg, 10mg , 15mg and 25 mg tablets available • 10 mg/day for the first 3 months, increased to 15 mg/day if tolerated, thereafter.
Cancer Treated	• newly diagnosed multiple myeloma following treatment with autologous stem-cell transplantation
Burden of Illness	• Myeloma is incurable in the vast majority of cases, with 1,350 deaths from the disease expected in Canada in 2013
Current Standard Treatment	• Autologous stem cell transplant is frequently performed as part of front line myeloma therapy in patients with multiple myeloma but is not curative • Thalidomide has been shown to prolong remission when administered as maintenance therapy post transplant, with some studies showing an overall survival advantage. • The role of bortezomib in the maintenance post-transplant setting has not been clearly defined.
Limitations of Current Therapy	• Older drug classes such as chemotherapy agents, corticosteroids and cytokines have not been found to significantly improve patient outcomes in the maintenance setting.

ABOUT THIS RECOMMENDATION

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

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

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

- Jo Nanson, Dr. Chaim Bell, Dr. Sunil Desai and Dr. Allan Grill who were not present for the meeting

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

Avoidance of conflicts of interest

All members of 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 lenalidomide (Revlimid) for multiple myeloma, through their declarations, two members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting.

Information sources used

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

Consulting publicly disclosed information

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

Use of this recommendation

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

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