pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Lenalidomide (Revlimid) for Newly Diagnosed Multiple Myeloma

January 14, 2016

Erratum: This is a revised Final Economic Guidance Report which supersedes the Final Economic Guidance Report for this drug and indication dated December 3, 2015. pCODR has provided more clarification on the Economic Guidance Panel's reanalysis of the post-progression benefit provided in the submitter's pharmacoeconomic model. The clarification does not change the overall conclusions of the Economic Guidance Panel or pERC's final recommendation.

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Celgene** compared lenalidomide (REVLIMID) to combination therapy (MPB: melphalan, prednisone and bortezomib) for patients with newly diagnosed multiple myeloma not eligible for stem cell therapy (SCT). Lenalidomide is administered orally while MPB is administered intravenously. The submitted economic analysis also presented a secondary analysis comparing continuous treatment with lenalidomide plus low dose dexamethasone (con-Ld) to melphalan prednisone and thalidomide (MPT).

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. The Provincial Advisory Group noted that the MPT comparator, as used in a secondary cost-effectiveness analysis, was not relevant for the Canadian setting. Additionally, according to the Clinical Guidance Panel, thalidomide is not a readily available treatment option in Canada. Therefore, the secondary analysis (con-Ld vs MPT) was not discussed further in this report.

Patients considered the following factors important in the review of lenalidomide which are relevant to the economic analysis:

- effective treatment which could reduce the likelihood of disease progression,
- choice of drugs based on known side effects, and
- potential improvements in quality of life.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for lenalidomide and which are relevant to the economic analysis. The main economic considerations were:

- The unknown duration of therapy with lenalidomide;
- High cost of lenalidomide compared to the current care standard.
- The necessity to monitor patients for potential adverse events while using lenalidomide;
- The lower cost of bortezomib now that it is available as a generic.

The PAG noted several other key aspects of this submission. First, the population that would receive this therapy would be relatively small. Second, oral administration of lenalidomide compared to intravenous bortezomib could be advantageous for some patients by reducing the necessity to travel frequently for therapy. This characteristic may also confer benefits to patients in rural settings. Third, the flat pricing of the different strengths of lenalidomide was seen as a barrier to implementation.

At the list price lenalidomide costs $340.00, $361.0, $382.00, $403.00, and $424.00 per 5, 10, 15, 20 and 25mg capsule, respectively. At the recommended dose of 25mg orally on days 1-21 per 28 day cycle, lenalidomide costs $318.00 per day and $8,904.00 per 28 day cycle.

At the list price, bortezomib (Velcade) costs $1,869.89 per 3.5mg vial. Based upon guidance from the pCODR Provincial Advisory Group (PAG), generic bortezomib is expected to cost $1402.42 per 3.5mg vial (at a 25% discount). The Economic Guidance Panel (EGP) and the submitted estimates are based on this expected generic price for bortezomib. At the recommended standard dose for cycles 1-4 (1.3mg/m^2 Days 1, 4, 8, 11, 22, 25, 29, 32 every 6 weeks) bortezomib costs $200.29 per day and $5608.08 per 28 day cycle. At the

recommended dose for cycles 5-9 (1.3 mg/m² Days 1, 8, 22, 29 every 6 weeks) bortezomib costs $100.17 per day and $2804.84 per 28 day cycle.

1.2 Summary of Results

The EGP did not provide a best estimate of con-Ld versus MPB, as con-Ld costs more and is no more effective than MPB (i.e., con-Ld is dominated). The Economic Guidance Panel based these results on the model submitted by the manufacturer and reanalyses conducted by the EGP (these results represent a truncated time horizon, equating progression-free health state utility values between con-Ld and MPB, equating post-progression benefit and the use of similar OS and PFS benefit) when lenalidomide is compared with bortezomib.

The EGP's re-analysis was based on the assumption that:

- the extra cost of lenalidomide is between $146,793 and $150,304. The main factors influencing the extra cost of lenalidomide are the unit cost of lenalidomide.
- based on the re-analysis conducted by the EGP, con-Ld did not have extra clinical effect, (i.e, 0 QALYs) when compared to MPB. The main factors influencing the incremental effects are the difference in overall survival between the two treatment regimens, a reduction of the difference in progression-free health state utility values, setting of post progression benefit between treatments to be the same and a truncated time horizon.

The EGP based these results on the model submitted by Celgene/Evidera and reanalyses conducted by the EGP. The greatest impact on the EGP's re-analysis was around assumption on the incremental benefit in survival. In the absence of a head-to-head trial and uncertainty in the assumptions of greater efficacy derived through a network meta-analysis (con-Ld vs MPB), the EGP in consultation with the CGP set the OS benefit to be equal between the two treatment regimens. While a randomised controlled trial is needed to confirm the true comparative efficacy between the two regimens, for the purpose of the economic analysis the conservative approach of equal efficacy and safety was deemed to be appropriate by the CGP. The reanalysis conducted by the EGP using the submitted model also included changes to other inputs as described below:

- When the time horizon is truncated at 10 years the extra cost of lenalidomide is $96,671, and the extra clinical effect is 0.67 QALYs, which increases the estimated incremental cost-effectiveness ratio to $145,221/QALY. When the time horizon is truncated at 20 years the extra cost of lenalidomide is $96,718, and the extra clinical effect is 0.94 QALY, which increases the estimated incremental cost-effectiveness ratio to $102,417/QALY.
- Equating the progression-free health state utility values between the two treatment regimens (set both to con-Ld estimate) resulted in an incremental cost of $102,826 and an incremental effect of 0.95 QALYs, increasing the ICER to $107,862/QALY.
- On guidance from the CGP and for the purposed of the economic evaluation, when a conservative estimate is used by setting the benefits of bortezomib containing therapy and lenalidomide containing therapy (in terms of overall survival and progression free survival) to be the same, the incremental costs were estimated to be $107,847 and the incremental effects, 0.09 QALYs, which resulted in a substantially increased ICER to $1,260,751/QALY.

- On guidance from the CGP, when the post-progression benefit was set to be equal between the two treatments the incremental costs were estimated to be $150,537 and the incremental effect, 0.75 QALY, which increases the ICER to $200,915/QALY.
- When combining the impacts of a 10 or 20 year time horizon with the above parameters, the extra cost associated with con-Ld is $146,793 or $150,304, respectively and the extra clinical effect is 0/QALY, resulting in an estimate of more cost and no incremental clinical effect (eg. con-Ld is dominated) in both scenarios.

Following the posting of the pERC Initial Recommendation which concluded that con-Ld is likely more effective than MPB, the EGP presented a sensitivity analysis to illustrate a scenario where con-Ld is more effective than MPB. In the absence of a randomised controlled trial to determine what the magnitude of this benefit may be to inform the economic evaluation, the EGP used the estimates for OS and PFS provided through a network meta-analysis prepared by Celgene. Limitations around the results of this NMA are presented in Section 7 of the Initial and Final Clinical Guidance Reports. The EGP noted that the estimates for the HR for OS were wide and ranged from an assumption of no difference in the risk of death to an estimate where the risk of death with con-Ld was half compared to MPB. The re-analysis estimates presented below were not included in the EGP's best estimates and are presented to demonstrate the uncertainty in the estimates of clinical effect between con-LD and MPB. These estimates represent a 'best-case' scenario in favour of con-LD therapy.

- To account for uncertainty in the estimates for OS and PFS, the EGP included a sensitivity analysis assuming greater efficacy with con-Ld compared to MPB by using the upper bound of the credible interval for the HR for OS and PFS derived from the network meta-analysis. This resulted in an incremental cost of $107,337 and an incremental effect of 1.66 QALYs, increasing the ICER to $64,650/QALY.
- When combining the above changes with changes to other parameters (10 year time horizon, equating the progression-free health state utility values between the two treatment, equating post-progression benefit between the two treatments), the extra cost associated with con-Ld is $93,005 and the extra clinical effect is 1.07 QALYs, resulting in an incremental cost effective ratio of $72,027/QALY.

The EGPs results varied substantially from the submitted estimates. The most significant impact that resulted in deviation from the Submitter's estimates was the effect of overall survival benefits conferred from lenalidomide containing therapy. When this assumption was altered based on CGP input, the ICER increased substantially from the Submitter's estimates.

According to the economic analysis that was submitted by Celgene/Evidera, when lenalidomide is compared with bortezomib:

- the extra cost of lenalidomide is $102,826 (ΔC). Costs considered in the analysis included costs of adverse event management (aneaemia, pneumonia, neutropenia, etc) and lab tests/monitoring.
- the extra clinical effect of lenalidomide is 1.02 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on extrapolated utility values from several trials (FIRST and VISTA (1,2)).

- the extra clinical effect of lenalidomide is 1.47 life years gained (ΔE). The clinical effect considered in the analysis was based on survival estimates from the FIRST trial (1) and a supplied network meta-analysis.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $100,784 per QALY or $69,871 per life year gained.

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

The main factors that resulted in a significant impact on the EGP's re-analysis as compared to the submitted estimates were those assumptions made around the incremental benefit gained with con-Ld. The EGP noted that the main source of data used to derive data between con-Ld and MPB was through a network meta-analysis. Following input from the CGP, the EGP varied several key model parameters to account for uncertainties around the estimates of comparative efficacy. First, the difference in OS and PFS between lenalidomide containing therapy and bortezomib containing therapy was deemed to be an overestimate. The CGP confirmed that without direct comparative evidence, there is uncertainty around the true incremental benefit conferred by lenalidomide. As a conservative approach and for the purpose of the economic analysis, the EGP used estimates of similar in efficacy for both OS and PFS. Therefore, re-analysis by the EGP reduced the OS and PFS effect to null. The CGP additionally noted that the time horizon should be truncated at 10 and 20 years to reflect a more plausible disease course for patients. Incremental benefit in the post-progression state was also set to be equal through CGP guidance, as there are no clinical data to support greater post-progression benefit for patients progressing on con- Ld. Finally, the difference in quality of life (progression- free health state utility values) between recipients of lenalidomide containing therapy and bortezomib containing therapy was thought to overestimate the benefit, therefore these were set to be equal. These changes all resulted in an estimate of 0 QALY (ΔE) and only extra cost (ΔE).

Were factors that are important to patients adequately addressed in the submitted economic analysis?

The main factors that were considered important to patients were included in the analysis. Patients desire therapies that can potentially reduce disease progression and the submitted analysis delineated between overall survival and progression-free survival. Improvements in quality of life were also important to patients and the submitted analysis addressed this by expressing outcomes in terms of quality-adjusted life-years. Finally, patients found it important to have a choice of drugs given the potential for side-effects and this submitted analysis allowed for switching between different types of therapies if a therapy was not well tolerated.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

The model structure appeared to be adequate for answering the question.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

The major assumptions made by the submitter are around the incremental benefit of con-Ld as compared to MPB. Changes in the hazard ratio for overall survival and progression free survival for bortezomib compared to lenalidomide resulted in substantial increases in submitted results. The setting of the HR for OS to be equal between con-LD and MPB had the single largest impact on the results. Additionally, the time horizon, assumed to be a lifetime time horizon (38 years), was truncated on advice of the CGP to reflect a more clinically plausible disease course for patients and this resulted in an increased the submitted results. Other assumptions that had an impact on the submitted results included: better quality of life for patients on lenalidomide (greater gains in progression-free health state utilities) and greater gains in post-progression benefit for patients progressing on lenalidomide after moving to subsequent therapies (post-progression benefit). The CGP confirmed that both scenarios were not clinically justifiable and the data presented to support these assumptions were not robust.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

No. The robustness of several parameter values were questionable - due to the lack of actual direct observed data - the CGP offered essential guidance on which inputs of clinical effect were appropriate. Overall, the CGP stated that there would not be substantial benefits in favour of the lenalidomide containing therapy over bortezomib containing therapy both in duration and quality of life. When these inputs were altered to reflect CGP guidance, there was no longer any incremental gain in efficacy and only extra cost associated with con- Ld. Model cost inputs, however, appeared to be adequate.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The provincial advisory group suggested and the CGP confirmed that MPT (thalidomide containing therapy) is not a relevant comparator in the Canadian context. The EGP therefore reduced the percentage of patients that would receive MPT and allocated these patients to receive lenalidomide. Based on the EGP's analysis, this resulted in a substantial increase in the budget impact. The market share of Ld was assumed to approximately double over the course of a 3-year period while MPB therapy would decline by approximately 25%. The result of this change in market share was a more than doubling of the budget impact by the third year. All other therapies in the analysis were assumed to be relatively stable over this period. A 25% increase in eligible patients for therapy, based on assumed base-case market share, would increase the incremental cost of adding con- Ld therapy by approximately $10 million over the course of 3 years. For Ld purposes, the EGP assigned all patients to receive either lenalidomide or bortezomib (50% each). This led to a substantial increase (more than double) in the budget impact.

What are the key limitations in the submitted budget impact analysis?

The budget impact analysis assumed that a proportion of patients were selected to receive MPT. This line of therapy was deemed to not be reflective of the Canadian experience. In

addition, a substantial proportion of patients were also assumed to be able to receive CYBORD therapy.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

There are several ways in which the submitted economic analysis could be improved:

- Health state utility values used to calculate QALYs are extrapolated (using several methods, depending on the treatment arm. It would be useful to have utilities associated with this specific condition and over time.
- The Submitter states that a survival partition model was used to avoid the limitations of Markov modeling, however, a discrete event simulation may have provided a better option.
- The MPT line of therapy (melphalan, prednisone, thalidomide) was not particularly relevant in the Canadian context as a component of the economic evaluation.
- Improved certainty pertaining to the robustness for progression-free survival and overall survival for bortezomib and lenalidomide would have been helpful. To adequately determine the true effect of lenalidomide containing therapy over bortezomib containing therapy, a proper clinical trial making a direct comparison between con- Ld and MPB should be undertaken to inform the pharmacoeconomic analysis.

Is there economic research that could be conducted in the future that would provide valuable information related to lenalidomide for newly diagnosed multiple myeloma?

The study could be improved by eliciting health state utility values specific to this patient population and on the relevant therapies, over the time horizon in this economic evaluation. Moreover, improved data on survival, thereby negating the necessity to rely on results of the network meta-analysis, would improve the robustness of this analysis.

2 DETAILED TECHINICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Lymphoma and Myeloma Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of Lenalidomide (Revlimid) for Newly Diagnosed Multiple Myeloma. A full assessment of the clinical evidence of Lenalidomide (Revlimid) for Newly Diagnosed Multiple Myeloma is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr)). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

REFERENCES

1. Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and Dexamethasone in Transplant-Ineligible Patients with Myeloma. N Engl J Med. 2014 Sep 4;371(10):906–17.

2. Delforge M, Dhawan R, Robinson D, Meunier J, Regnault A, Esseltine D-L, et al. Health-related quality of life in elderly, newly diagnosed multiple myeloma patients treated with VMP vs. MP: results from the VISTA trial. Eur J Haematol. 2012 Jul 1;89(1):16–27.

3. Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies Canada. [Internet]. Ottawa, Ont.: Canadian Agency for Drugs and Technologies in Health; 2006 [cited 2015 Apr 8]. Available from: http://site.ebrary.com/id/10119368

4. KMF investigators, Kobayashi T, Kuroda J, Fuchida S, Kaneko H, Yagi H, et al. Impact of early use of lenalidomide and low-dose dexamethasone on clinical outcomes in patients with relapsed/refractory multiple myeloma. Int J Hematol. 2015 Jan;101(1):37–45.