pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Lenalidomide (Revlimid) for Multiple Myeloma

October 22, 2013

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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 placebo for patients with multiple myeloma (MM) following chemotherapy and autologous stem cell transplantation (ASCT**). Lenalidomide is administered orally. At present, there is no agreed upon standard maintenance therapy following ASCT and thus supportive care was used as the comparator in the evaluation. The analysis was based on the CALGB100104 study, which compared lenalidomide maintenance plus best supportive care with placebo plus best supportive care. The key NEJM publication was based on a data cut-off of 31 October 2011, but the economic evaluation was based on a data cut-off of July 2012, allowing almost 1 more year of follow-up.

According to the pCODR Clinical Guidance Panel (CGP), there is no currently accepted standard for maintenance therapy following ASCT, and thus the use of supportive care (placebo) as the comparator is appropriate.

Patients considered the following factors important in the review of lenalidomide, which are relevant to the economic analysis: the incidence and control of infections, kidney problems, pain, mobility, neuropathy, and shortness of breath and fatigue. The model included the incidence of infection with the lenalidomide and placebo, but did not explicitly consider the other factors. A full summary of patient advocacy group input is provided in the pCODR Clinical Guidance Report.

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: PAG acknowledged that there are no drugs currently approved for maintenance therapy, but noted that bortezomib and/or thalidomide may be used in some jurisdictions. The PAG would like to see a comparison of lenalidomide with these drugs, but no economic comparison was submitted. The PAG also expressed concerned with the flat pricing across the four different strengths. A patient on 10mg tablets whose dose was increased to 15mg in the form of a 10mg tablet + 5 mg tablet to allow for further dose adjustments would cost twice that of a patient on 15mg tablets. Finally, there was concern that demand for lenalidomide maintenance therapy would continue beyond MM disease progression. A full summary of PAG input is provided in the pCODR Clinical Guidance Report.

Lenalidomide has a relatively flat pricing structure that changes very little as dosage increases. A 5mg tablet costs $340; a 10mg tablet costs $361; a 15mg tablet costs $382; and a 25mg tablet costs $424. The 5mg and 10mg tablets are dispensed in 28-count packs at a cost of $9520 and $10,108 per pack, respectively, and the 15mg tablets are dispensed in 21-count packs at a cost of $8022 per pack. At the recommended dose of 10-15mg lenalidomide costs $361 to $382 per day and the average cost per 28-day cycle is between $10,108 and $10696.

1.2 Summary of Results

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $171,702 and $183,366 when lenalidomide is compared with placebo.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- the extra cost of lenalidomide is between $279,032 and $279,657 (ΔC). The key cost driver was the cost of the drug itself, although the model suggested that lenalidomide was associated with relative cost savings in the post-progression period.
- the extra clinical effect of lenalidomide is between 1.53 and 1.77 quality-adjusted life years (QALYs) (ΔE). However, a substantial proportion (28%) of the QALY gains with lenalidomide comes from a survival advantage in the post-progression phase, which may not be supported by the clinical evidence.
- Costs and outcomes were discounted by 5% per year to account for time preferences that value costs and benefits in the present more highly than those in the future.

The EGP based these estimates on the model submitted by manufacturer and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- the analysis horizon is truncated at 15 years, the extra cost of is $279,032 ($\Delta C_1$), which increases the estimated incremental cost-effectiveness ratio to $171,702.
- the model excludes the post-progression survival advantage of lenalidomide, the extra clinical effect of lenalidomide decreases to 1.53 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $183,366.
- Costs and outcomes were discounted by 5% per year to account for time preferences that value costs and benefits in the present more highly than those in the future.

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by the manufacturer, when lenalidomide is compared with placebo:

- the extra cost of lenalidomide is $279,657 (ΔC). Costs considered in the analysis included drug acquisition costs, laboratory monitoring costs and post-progression costs.
- the extra clinical effect of lenalidomide is 2.43 discounted life years (LYs) and 1.77 discounted quality-adjusted life years (QALYs) (ΔE). The clinical effect considered in the analysis was based on a longer time to disease progression, and improved survival in the post-progression phase.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $114,887 per LY gained and $158,129 per QALY 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 key difference between the manufacturer's estimates and the EGP estimates were around the post-progression survival advantage of lenalidomide. The manufacturer's model shows that 31% of the life year gains and 28% of the QALY gains occurred in the post-progression phase, but the CGP felt that there was little clinical reason to suspect that lenalidomide should provide such a substantial survival benefit post-progression. In addition, the key clinical trial does not clearly distinguish between survival in the pre- and post-progression phases. As such, CGP recommended a reanalysis based on the pre-progression survival advantage only. Also, the time horizon in the manufacturer's model was approximately 40 years, which CGP felt may to be too long for this clinical setting, and suggested a 15-year horizon. See the detailed technical report for an explanation of the effect of an overly-long analysis horizon.

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

The patient input noted the incidence and control of infections, kidney problems, pain, mobility, neuropathy, and shortness of breath and fatigue as important factors in the consideration of lenalidomide. The model included the incidence of infection with the lenalidomide and placebo, but did not explicitly consider the other factors, although CGP noted that most of these factors are associated with multiple myeloma in general, rather than a specific drug therapy, and therefore are unlikely to differ by treatment.

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

The model is adequate for summarizing the evidence, although there are some notable limitations. First, progression-free and overall survival in the lenalidomide and placebo arms were analysed using a partitioned survival model, considering the two arms independently with no formal relationship between them. This provides the best parametric fit, but makes it very difficult to test different assumptions about the relative efficacy of lenalidomide. The manufacturer included sensitivity analyses allowing for relatively better and worse estimates of the effectiveness of lenalidomide compared to placebo, but these results could not be confirmed by EGP.

Given the concerns with the appropriateness of the post-progression survival gains, it should be noted that the model did allow for different assumptions around the post-progression survival advantage, and EGP was able to conduct a re-analysis excluding post-progression benefits

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 post-progression survival advantage was driven by the parametric modelling of overall and progression-free survival. Although such modelling is necessary to extend the results beyond the relatively short horizon of the clinical trial, CGP was skeptical of the survival advantage implied by these projections. The model assumed an improvement in overall survival in favour of lenalidomide of a magnitude of slightly more than 4 years (undiscounted), but according to CGP, the IFM 2005-02 study did not show statistically

significant overall survival improvement, while the CALGB 100104 study reported a statistically significant in favor of lenalidomide. Therefore, it is unclear whether the true magnitude of overall survival benefit of lenalidomide is about 4 years or if it may be substantially less. The analysis adopted a 40-year horizon, which CGP felt may be too long in this clinical setting. EGP re-analysis suggested that adopting a shorter horizon would have an adverse impact on relative cost-effectiveness. The model also assumed that EQ-5D utility weights from an external population of patients with MM treated with intensive chemotherapy with or without ASCT –- but not lenalidomide specifically -- were representative of the patients in the key clinical trial. The methods used to elicit these utility weights were reasonable, but changing the source of the utility weights had a notable impact on the cost-effectiveness estimates, highlighting the sensitivity of the results to the source of these weights.

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?

The cost estimates appeared appropriate, and although the source of the clinical efficacy estimates was appropriate, the parametric projection of the short-term trial outcomes may overstate survival gains. Quality-of-life should have been collected as part of the clinical trial, particularly as the results appear reasonably sensitive to the source of the utility weights.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The generic budget impact analysis is most strongly influenced by the expected number of post-transplant multiple myeloma cases eligible for maintenance therapy, as well as the cost of lenalidomide therapy. Both of these parameters are clearly identified in the BIA and can easily be adjusted by the analyst. The BIA model allows for the concerns expressed by the PAG around the pricing structure of lenalidomide, and the expected duration of therapy, to be tested.

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

The BIA is a generic analysis, and leaves it for the appropriate provincial decision-makers to estimate the relevant populations. All parameters are easily edited, allowing for a flexible analysis. There are no notable limitations, beyond the generic nature of the initial parameters.

1.5 Future Research

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

Future research should consider the role of partitioned survival analysis compared to state-transition models in economic evaluations. Although partitioned survival analysis can

provide a better parametric fit than a proportional hazards analysis, the resulting model is much less flexible in terms of allowing for testing different efficacy relationships.

Is there economic research that could be conducted in the future that would provide valuable information related to lenalidomide for patients with multiple myeloma (MM) following chemotherapy and autologous stem cell transplantation (ASCT)?

Quality-of-life data used to inform the economic analysis should be collected directly from the population under study.

2 DETAILED TECHNICAL 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 Final Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR 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 multiple myeloma. A full assessment of the clinical evidence of lenalidomide (Revlimid) for 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.pcodr.ca).

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. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

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.pcodr.ca). 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.

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