PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Pomalidomide (Pomalyst) for Multiple Myeloma

July 31, 2014

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Celgene Inc.** compared pomalidomide 4mg plus low dose dexamethasone 40mg (Pom-LDex) to best supportive care (BSC) for patients with relapsed or refractory Multiple Myeloma (rrMM). The comparator BSC arm was constructed as a combination of therapy options each weighted by its average usage. The patient population reflects the overall population of the MM-003 Study [1] This study was implemented on adult patients with documented and measurable refractory or relapsed and refractory multiple myeloma, with ECOG performance score 0-2, and who have undergone at least 2 prior treatment lines, including having received at least 2 consecutive cycles of prior treatment that included lenalidomide and bortezomib, either alone or in combination. All patients must have failed prior lenalidomide and bortezomib treatment. Pomalidomide and dexamethasone are administered orally while the route of administration for the BSC arm varies depending on the treatment alternative.

According to the pCODR Clinical Guidance Panel (CGP), comparison with BSC is appropriate. However, the definition of BSC by the CGP differs to that of the submitter of the economic analysis. Given the absence of robust clinical evidence suggesting the superiority of alternative options over high dose dexamethasone and the difficulty of understanding how reflective the other options are of actual Canadian clinical practice, BSC according to the CGP would include mainly HDex. Oppositely, the submitter defined BSC as a combination of a number of possible interventions (e.g. Lenalidomide+Dex, Bortezomib+Dex, stem cell transplantation, palliative care) each weighted by an estimate of its average usage.

Patients considered the following factors important in the review of pomalidomide, which are relevant to the economic analysis: Components of quality of life (QoL) such as mobility and pain, health outcomes such as infections and control of disease progression and side effects due to pomalidomide. The components associated with QoL were taken into account by incorporating QoL estimates from the clinical trial in the economic evaluation. The control of disease progression, infection rates and the number of serious adverse events were also taken into account in the submitted economic analysis.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for pomalidomide, and which are relevant to the economic analysis: the fact that pomalidomide is available in a convenient means of administration (oral). The PAG stressed the importance of monitoring for toxicities including neutropenia and venous thromboembolism. PAG also noted the potential cost implication with flat pricing of pomalidomide to be a barrier.

At the list price, pomalidomide costs $500.00 per 1mg, 2mg, 3mg and 4mg capsule. At the recommended dose of 4mg orally on days 1-21 of 28-day cycle, for a 70 kg patient, pomalidomide costs $375.00 per day and $10,500.00 per 28 day course. Since the pomalidomide capsule is flat priced, depending on the combination of capsules used to provide a 4mg dose, the price of pomalidomide may be as high as $1500 per day and $42,000 per 28 day course.

Dexamethasone costs $0.3046 per 4mg tablet. At the recommended dose 40 mg on days 1, 8, 15, 22 (low dose dexamethasone) and 40mg on days 1-4, 9-12, and 17-20 (high dose dexamethasone), low dose dexamethasone costs $0.4351 per day and 12.3200 per 28 day and high dose dexamethasone costs $1.3054 per day and $36.5520 per 28 day course.

1.2 Summary of Results

Because of the discrepancy between what the CGP defined as appropriate comparator, the comparator assumed in the submitted economic analysis and the available evidence, the EGP considered BSC with HDex as the comparators in the base case analysis. The rationale behind this choice is that BSC with HDex is the closest treatment option to what the CGP suggested as an appropriate comparator. The EGP provides below a range of best estimates due to uncertainties related to the submitted input evidence. In particular, the range reflects the uncertainty around the assumptions of the model's time horizon (10 years vs 5 years) and the assumption of a sustained effect of Pom-LDex on overall survival after the cut-off date of the RCT (effect sustained for 2 years vs no sustained effect)

The EGP's best estimate of the incremental cost-effectiveness ratio between pomalidomide-low dose dexamethasone (Pom-LDex) and BSC with HDex is between $132,217/QALY (10 year time horizon assumption, effect on overall survival sustained for 2 years after the cut-off date) and $173,430/QALY (5 year time horizon, no effect on overall survival after the cut-off date).

The EGP's best estimate of:

- the extra cost of Pom-LDex is estimated to be between $67,397 and $70,208 . The main factor contributing to this cost is the cost of therapy with Pom-LDex.
- the extra clinical effect of Pom-LDex is estimated between 0.39 QALYS and 0.53 QALYs. The main factor contributing to this extra clinical effect is the reduced risk of progression for Pom-LDex as well as a sustained effect of Pom-LDex post-progression.

The EGP based these estimates on the model submitted by Celgene inc and reanalyses conducted by the EGP and the submitter after request of the EGP.

The reanalyses conducted by the EGP using the submitted model showed that when:

- Pom-LDex is compared to BSC with HDex, the extra cost of Pom-LDex is between $67,397 and $70,208, which increases the estimated incremental cost-effectiveness ratio (between $132,217/QALY and $173,430/QALY).

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Celgene inc., when Pom-LDex is compared with BSC (as defined by the submitter):

- the extra cost of Pom-LDex is $44,858. Costs considered in the analysis included therapy costs, treatment of adverse events oncologist visits and transfusions.
- the extra clinical effect of Pom-LDex is 0.53/0.77 [quality-adjusted life years/life years gained(LYG). The clinical effect considered in the analysis was based on estimates of overall survival, progression free survival and quality of life all coming from the same randomized controlled trial.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $58,008/LYG or $84,476/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 EGP estimates differ from the submitter's due to differences in the assumptions of comparator, time horizon and residual effect of the drug on overall survival after progression. The submitter has assumed as BSC a combination of alternatives weighted according to their usage in clinical practice. The submitter applied different costs to each BSC alternative but assumed similar effectiveness across all of them. The EGP reanalyzed separate models by assuming BSC with HDex as the comparator instead of the submitted weighted comparators. In addition the EGP conducted reanalyses, based on suggestions by the CGP, where the model's time horizon was shortened to 5 years to reflect better the life expectancy of the underlying patient population. Finally, in the base case analysis the assumption of a sustainable effect of Pom-LDex on survival after the MM-003 RCT's cut-off date was varied between 2 years and no sustainable effect. The assumption of a sustained effect after the cut-off date implies that Pom-LDex will have an effect on prolonging survival post-progression, since by the cut-off date of the trial the vast majority of patients had progressed in both arms. Under this assumption, the submitter identified a life time effect of Pom-LDex on life expectancy of 0.77 life years gained (LYG), of which nearly 70% happened post progression. The CGP suggested that there is no known clinical justification for such a post-progression residual benefit. To adjust for this assumption the EGP conducted a reanalysis where no sustained effect was assumed after the cut-off date of the trial.

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

The submitter has addressed the majority of the concerns of the patient advocacy group. Quality of life was taken into consideration as well as the toxicity and other adverse events related to treatment with Pom-LDex. Additionally, the impact of Pom-LDex on survival and progression free survival was taken into account in the economic model.

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

The economic analysis was based on a partitioned survival model. This model relies directly on the estimates of progression-free and overall survival to estimate the probability of patients remaining in any of the three assumed states (progression-free, progression, death). This model was properly constructed for a partitioned survival model; however there were limitations on the extent of reanalysis that could be conducted by the EGP.

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 study that supported the economic analysis with clinical evidence allowed for patients in the control arm to cross over to the Pom-LDex arm. The submitter has adjusted the estimates of overall survival to accommodate the crossover design. However there is limited information in the submitted report and the economic model on the exact procedure and the impact of cross-over on the estimates of OS. The EGP estimated that the method of correction used might have an important effect in the analysis. Additionally, as mentioned above the choice of comparator was not in agreement with the

CGP's suggestion as the most relevant comparator. This assumption had a significant effect on the outcome, as suggested by the reanalyses conducted by the EGP. Finally, the submitter assumed a statistically and clinically significant reduction in utility after transitioning to a progressed state. However the data from the MM-003 study did not identify such a significant effect. Assuming no significant disutility associated with progression would increase the ICER of Pom-LDex. Finally, the assumption of a time horizon of 10 years was considered unreasonable by the CGP, with 5 years being more appropriate. The rest of the submitter's assumptions in the economic model are reasonable. Some of the uncertainties with respect to unclear assumptions that were made in the model were resolved after the submitter was requested to do so by the EGP. The EGP also conducted a number of additional reanalyses, however not all concerns could be tackled through them. Uncertainty was in general appropriately taken into consideration in the economic analysis.

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 and clinical effects estimates that were used by the submitter in the submitted economic model and the models analyzed by the EGP models were similar. The only cost parameters that the EGP utilized differently were those associated with the control treatment as the EGP looked at individual treatment options and not a weighed BSC option.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

A budget impact analysis (BIA) was submitted to determine the impact of the introduction of Pom-LDex in the healthcare system over a three year time horizon. The budget impact was conducted from the public payer's perspective. The factors that play the most important role on the budget impact were the disease prevalence, the duration of treatment, the proportion of patients covered by a drug plan and the market share of pomalidomide.

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

The BIA model presented by the submitter is based on a large number of assumptions either from the literature or from expert opinion. Specifically, identifying the correct proportion of patients that are refractory to multiple myeloma is challenging. Additionally, as the submitter mentions the model assumes that the current standard of care for patients that are refractory to lenalidomide and bortezomib results in no additional costs. This is not in line with the assumptions of the economic model where the comparator on the submitted economic model was BSC. This overestimates the budget impact of Pom-LDex which is a conservative assumption.

1.5 Future Research

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

The study could benefit from more accurate estimates of OS, PFS and QoL for all comparators assumed by the EGP.

Is there economic research that could be conducted in the future that would provide valuable information related to Pom-LDex?

The current economic evaluation is using QoL estimates that were extracted alongside a clinical trial. As the submitter pointed out the MM-003 study was not powered to show a significant difference. The analysis could be improved by using health related QoL estimates extracted from a study that is specifically designed to provide QoL estimates. Additional data on the effectiveness of other interventions that were considered by the submitter for the BSC arm would improve the accuracy of the economic analysis

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 pomalidomide (Pomalyst) for multiple myeloma. A full assessment of the clinical evidence of pomalidomide (Pomalyst) 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.

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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