PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Final Economic Guidance Report

Erratum: This is a revised Final Economic Guidance Report which supersedes the Final Economic Guidance Report for this drug and indication dated May 19, 2015. The revision does not impact the Final Clinical Guidance Report or the Final pERC Recommendation. The change impacts the upper bound of the Economic Guidance Panel's best estimate of the ICER.

Romidepsin (Istodax) for Peripheral T-Cell Lymphoma

July 28, 2015

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FUNDING

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Celgene Inc.** compared romidepsin (Istodax®) to currently available treatments (referred to herewith by the EGP as the "comparator") for patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) who are not eligible for transplant and have received at least one prior systemic therapy. Romidepsin is administered intravenously at a dose of 14 mg/m^2 on days 1, 18 and 15 of a 28-day cycle. As the trial from which the clinical information for romidepsin was a single-arm study, data was collected from the British Columbia Cancer Agency to inform the comparator arm. The comparator was a mix of polychemotherapy drugs and included GDP (gemcitabine, cisplatin, dexamethasone), GemOx (gemcitabine, oxaliplatin) and ICE (ifosfamide, carboplatin, etoposide).

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate, however, there is no one standard of care treatment regimen across Canada and this may not reflect the treatment present at all centers. The Clinical Guidance Panel considered that brentuximab may also be included as part of the standard of care treatment mix. The Submitter did not include this comparison in modifications to the main economic analysis.

Patient advocacy group input was not available for this submission. However, through a search of the literature, patient-relevant factors were identified. Patients stated that they wanted increased overall survival, progression-free survival, and quality of life through the availability of additional treatments. Patients stated that they were willing to tolerate side effects to achieve these goals. Only overall survival and quality of life was incorporated into the economic model. Progression-free survival and adverse events were not available for the comparator arm, and were therefore not considered.

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

Enablers to the implementation of romidepsin include:

- New class of drug that could fill the gap in therapy for patients with PTCL who have received one prior therapy.
- Very small eligible patient population.

Barriers to the implementation of romidepsin include:

- No comparative trials between romidepsin and other therapies currently in use.
- Unknown duration of treatment, as patients have the option to continue treatment beyond the recommended six cycles. The economic model considers treatment up to 62 cycles, based on data from the study.
- Administration as an intravenous drug may be a barrier for those not near an outpatient chemotherapy center. Further, this administration has increased administration costs associated with it (which are considered in the economic model).
- Drug wastage given the availability of only one vial size and the short stability of the vial after reconstitution. Drug wastage was considered as part of the main analysis.

Romidepsin costs $2,582 per 10 mg vial. At the recommended dose of 14 mg/m^2 on days 1, 8 and 15 of a 28-day cycle, assuming no vial sharing, romidepsin costs $658.41 per day and $18,435.48 per 28 day cycle.

1.2 Summary of Results

Following the identification of an error, which resulted in an incorrect upper bound of the EGP's estimate, the report was revised to reflect this correction. The error involved macros in the Excel model, and resulted when several model parameters were changed simultaneously. All other estimates have been verified for accuracy, to the best of the EGP and pCODR knowledge.

The EGP's best estimate of the incremental cost-utility ratio (ΔC / ΔE) is between $217,588 and $387,056 (UPPER BOUND ERROR CORRECTED) when romidepsin is compared with the comparator treatment mix, though it is unlikely that the ICUR is near the upper bound.

The incremental cost-utility 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 romidepsin is between $105,224 and $144,434. The main factors affecting cost are the number of patients treated and overall survival.
- the extra clinical effect of romidepsin is between 0.3207 and 0.4836 (ΔE). The main factors affecting clinical effects is overall survival and utilities.

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

- The time horizon was changed from 20 years to 10 years, based on feedback provided by the clinical guidance panel, the extra cost of romidepsin is $102,235 ($\Delta C_1$), and the extra clinical effect of romidepsin is 0.5182 (ΔE_1), which increases the estimated incremental cost-utility ratio to $197,271 (from $186,253).
- Wastage was taken into account, as calculated by the EGP using a weighted analysis, the extra cost of romidepsin is $105,255 ($\Delta C_2$), and the extra clinical effect of romidepsin is 0.5491 (no change from baseline), which increases the estimated incremental cost-utility ratio to $191,271 (from $186,253).
- Utilities decreased as disease progressed (instead of a constant utility score throughout the economic model), the extra cost of romidepsin is $102,266 (no change from baseline), and the extra clinical effect of romidepsin is 0.5106 (ΔE_2), which increases the estimated incremental cost-utility ratio to $200,272 (from $186,253).
- The best case estimate of the above three parameters is $217,588, with an extra cost of romidepsin of $105,224 (ΔC) and an extra clinical effect of romidepsin of 0.4836 (ΔE).
- The upper 95% confidence interval of the number of patients treated is considered, as there is uncertainty in how many patients will be treated for how long (based on feedback from the CGP), the extra cost of romidepsin is $145,320 ($\Delta C_3$), and the extra clinical effect of romidepsin is 0.5491 (ΔE_3), which increases the estimated

incremental cost-utility ratio to $264,666 (from $186,253). It should be noted that the 95% confidence intervals for number of patients treated were very wide, therefore, though the EGP uses this upper interval as part of their upper bound for the best estimate, it is unlikely to reflect clinical practice.

- The best case estimate of the above four parameters is $308,852, with an extra cost of romidepsin of $149,359 (ΔC) and an extra clinical effect of romidepsin of 0.4836 (ΔE).
- Overall survival is based on the Kaplan Meier curves, and not on extrapolation using parametric curves, the extra cost of romidepsin is $97,700 ($\Delta C_3$), and the extra clinical effect of romidepsin is 0.3018 (ΔE_3), which increases the estimated incremental cost-utility ratio to $323,775 (from $186,253).
- The best case estimate of the above five parameters is $387,056, with an extra cost of romidepsin of $144,434 (ΔC) and an extra clinical effect of romidepsin of 0.3207 (ΔE). The EGP notes that the ICUR will not likely fall in the upper range, for the same reasons stated above, that the number of patients treated would most likely not be the number reflected by the wide 95% confidence intervals.

The EGPs estimates differed the submitted estimates.

According to the economic analysis that was submitted by Celgene Inc, when romidepsin is compared with the standard of care:

- the extra cost of romidepsin is $102,266 (ΔC). Costs considered in the analysis included drug costs, administration costs and ongoing medical care.
- the extra clinical effect of romidepsin is 0.55 quality-adjusted life years (ΔE) and 0.68 life years (ΔE). The clinical effect considered in the analysis was based on overall survival, time on treatment and utilities.

So, the Submitter estimated that the incremental cost-utility ratio (ΔC / ΔE) $186,253 per QALY or $150,716 per life year gained.

1.3 Summary of Economic Guidance Panel Evaluation

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

The main reasons for the difference in the ICUR was the manipulation of the time horizon, modeling of overall survival, number of patients treated and modeling of utilities. Based on feedback from the clinical guidance panel, the EGP felt that a 10-year time horizon was more appropriate, given the number of patients alive after 10 years. Further, using a constant value for utilities was not reflective of clinical practice; the EGP selected the modeling of utilities based on decreasing values as a function of time. The clinical guidance panel confirmed that this is reflective of what is seen in patients: their quality of life worsens as they approach death. Based on input from the Clinical Guidance Panel, the EGP noted that there is uncertainty in the number of patients treated with romidepsin in any given cycle. To account for this, the EGP used the upper bound of the 95% CI for number of patients treated in the trial, as there was uncertainty in cost if more patients were treated. Finally, the EGP felt that there was a heavy reliance on extrapolation for overall survival data (given the length of the clinical trial) and that the estimates for

median overall survival were not aligned with the observed overall survival. Therefore, the Kaplan-Meier curves were selected for the overall survival, instead of extrapolating using a parametric curve.

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

The patient-relevant factors identified through the literature that were incorporated included overall survival and quality of life. Patients had also identified progression-free survival and side effects as being important, however, these were not included as these data inputs were not available for the comparator arm.

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

Yes, the model was adequate. However, an economic model that incorporates more than two health states (alive and dead) would better reflect clinical practice. Many of the other assumptions in the economic model were able to be examined using sensitivity analyses. It should also be recognized that the structural limitations of the model were due to limitations in the data inputs and not merely a lack of desire to increase the complexity of the model.

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?

Overall survival, and the way in which it was modeled, had a substantial impact on the results. The submitter chose to present a main analysis that relied on extrapolation of data, fitted to a parametric curve. The EGP felt that this was not appropriate given the length of the clinical trial, and the amount of extrapolation. The number of patients treated (using the 95% confidence intervals provided by the submitter) also had a substantial impact on the ICUR.

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?

Estimates of clinical effects were reasonable given the type of data available. There were limitations in the amount of data available as no head-to-head clinical trials were done between the treatment and the current standard of care. Further, the source of data the submitter used to inform the comparator arm could not provide information on progression-free survival nor adverse events. Therefore, these inputs were not considered in the economic model. It is unknown if these inputs would have substantially impacted the ICUR. Estimates of costs used in the economic model were adequate.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The largest cost drivers of the budget impact analysis are the predicted market shares of romidepsin, proportion of patients with PTCL among those with non-Hodgkin's lymphoma and the cost of romidepsin.

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

Given the limited availability of data around the number of patients with PTCL, the prevalence of PTCL was estimated by multiplying the incidence of PTCL by an average overall survival of 2 years. The CGP indicated that 1 year was more likely, however, 2 years was a conservative estimate. The submitter estimated that six cycles of treatment were planned; the maximum treatment duration observed in the clinical trial was 62 cycles. The PAG noted that this may be an issue as many patients continue on treatment beyond response.

1.5 Future Research

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

When providing an economic model, all sheets and data should be present. This would avoid having to "unhide" certain important information. Further, a model that incorporates more health states would reflect clinical practice. Though the EGP recognizes that data was not available to inform all health states, alternatives should be examined as there is much more to modeling disease other than "alive" and "dead". Further, it is always ideal to allow manipulation of the 95% confidence intervals around overall survival, without modifying the shape and scale of the curve.

Is there economic research that could be conducted in the future that would provide valuable information related to romidepsin for PTCL?

Given the challenges with the limited number of patients affected by this disease per year, and the lack of standard of care for this patient group, it is difficult to identify one area of research for this patient population.

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 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 Romidepsin (Istodax) for Peripheral T-Cell Lymphoma. A full assessment of the clinical evidence of Romidepsin (Istodax) for Peripheral T-Cell Lymphomais 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.

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