pan-Canadian Oncology Drug Review
Initial Economic Guidance Report

Ramucirumab (Cyramza) for Gastric Cancer

September 3, 2015

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FUNDING
The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

There were two main economic analyses that were **submitted to pCODR by Eli Lilly.** The first analysis compared ramucirumab plus paclitaxel to placebo plus paclitaxel for patients with advanced or metastatic gastric cancer or gastro-esophageal junction cancer (GC/GEJC) with a European Cooperative Oncology Group (ECOG) performance status of 0 – 1 and who have received prior chemotherapy. The second analysis compared ramucirumab plus best supportive care to placebo plus best supportive care for patients with advanced or metastatic GC/GEJC with a ECOG performance status of 0-1 and for whom chemotherapy is not a preferred treatment strategy. Ramucirumab is administered intravenously, as is paclitaxel.

According to the pCODR Clinical Guidance Panel (CGP), the comparator of paclitaxel is appropriate; however, the comparator of best supportive care is of limited appropriateness for a population with a good performance status (i.e., ECOG 0-1).

Patient advocacy group input was not provided for this submission. A literature review conducted by pCODR identified the following factors important to patients in the review of ramucirumab, which are relevant to the economic analysis: adverse events, extended survival and increased quality of life. All three of these factors were incorporated into the economic analysis.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for ramucirumab:

- Wastage: this was incorporated into the base case analysis from the submitter and was not altered by the EGP.
- Administration costs of paclitaxel: administration costs for all drugs were considered in the submission.
- Clinical benefit of monotherapy versus in combination with paclitaxel: two separate economic models were submitted, one for ramucirumab monotherapy and one for ramucirumab plus paclitaxel. These models did not have the same comparators. Therefore, the relative benefits of ramucirumab monotherapy vs ramucirumab plus paclitaxel, relative to each other, has not been assessed; their benefit has only been assessed relative to their comparators (best supportive care or paclitaxel).

The PAG noted that the cost of the drug, its administration and any additional monitoring of patients for adverse events is a barrier; the addition of another option of treatment for these patients is an enabler.

At the list price, ramucirumab costs $909.42 per 100 mg vial or $4547.10 per 500 mg vial. At the submitted confidential price, ramucirumab costs $[redacted] per 100 mg/ml vial or $[redacted] per 500 mg/ml vial. *(The cost of ramucirumab is based on a confidential price submitted by the manufacturer and cannot be disclosed to the public according to the pCODR Disclosure of Information guidelines.)* For ramucirumab monotherapy, the recommended dose is 8 mg/kg every 2 weeks. Ramucirumab in combination with paclitaxel is given at a recommended dose of 8 mg/kg on days 1 and 15 of a 28-day cycle, prior to paclitaxel infusion. Paclitaxel costs $394.12 per 6 mg/mL 5mL vial, $1,258.67 per 6 mg/mL 16mL vial or $3,941.24 per 6 mg/mL 50 mL vial. The recommended dose is 80 mg/m^2 on days 1, 8 and 15 of a 28-day cycle. The EGP noted that the price of paclitaxel may be quite significantly lower in Canadian jurisdictions than that used in the Submitter's model.

1.2 Summary of Results

Ramucirumab plus paclitaxel vs placebo plus paclitaxel

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $432,159 and $490,437 when ramucirumab plus paclitaxel is compared with placebo plus paclitaxel.

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 ramucirumab plus paclitaxel is between $38,732 and $43,955. The factors that had the biggest impact on extra cost were length of stay of patients in hospital, the daily cost of hospitalization and the probability of hospitalization.
- the extra clinical effect of ramucirumab plus paclitaxel is 0.09 (ΔE). The factors chosen by the EGP in the best estimate did not change the extra clinical effect.

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

- The length of stay in hospital input was taken from all patients, by treatment arm, and not just those from Region 1, the extra cost of ramucirumab plus paclitaxel is $10,308 ($\Delta C_1$), which decreases the estimated incremental cost-effectiveness ratio to $115,008 (from $332,628).
- Body weight and body surface area of patients was taken from all patients, and not just those from Region 1, the extra cost of ramucirumab plus paclitaxel is $25,518 ($\Delta C_2$), which decreases the estimated incremental cost-effectiveness ratio to $284,725 (from $332,628).
- The probability of hospitalization is based on observed & unadjusted data, the extra cost of ramucirumab plus paclitaxel is $58,238 ($\Delta C_3$), which increases the estimated incremental cost-effectiveness ratio to $649,799 (from $332,628).
- The daily cost of hospitalization is increased by 25%, the extra cost of ramucirumab plus paclitaxel is $23,244 ($\Delta C_4$), which decreases the estimated incremental cost-effectiveness ratio to $259,346 (from $332,628).
- The daily cost of hospitalization is reduced by 25%, the extra cost of ramucirumab plus paclitaxel is $36,380 ($\Delta C_5$), which increases the estimated incremental cost-effectiveness ratio to $490,437 (from $332,628).

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Eli Lilly, when ramucirumab plus paclitaxel is compared with paclitaxel plus placebo:

- the extra cost of ramucirumab plus paclitaxel is $29,812 (ΔC). Costs considered in the analysis included the cost of the drug, medical resource use costs and other costs associated with treatment.

- the extra clinical effect of ramucirumab plus paclitaxel is 0.09 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on overall survival, progression-free survival, adverse events and utilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $332,628 / QALY.

Ramucirumab plus best supportive care vs placebo plus best supportive care

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $414,351 and $491,079 when ramucirumab plus best supportive care is compared with placebo plus best supportive care.

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 ramucirumab plus best supportive care is between $46,244 and $54,807. The factors that had the biggest impact on extra cost were length of stay of patients in hospital, the daily cost of hospitalization and the parametric function to model progression-free survival.
- the extra clinical effect of ramucirumab plus best supportive care is 0.11 (ΔE). The factor that impacted the clinical effect in the best case estimate was the parametric function to model progression-free survival.

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

- The parametric function to model progression-free survival was based on the Weibull curve, the extra cost of ramucirumab plus best supportive care is $42,654 ($\Delta C_1$) and the extra clinical effect is 0.11 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $382,184 (from $353,965).
- The input for length of stay in hospital was taken from all patients, by treatment arm, and not just those from Region 1, the extra cost of ramucirumab plus best supportive care is $49,408 ($\Delta C_2$), which increases the estimated incremental cost-effectiveness ratio to $428,987 (from $353,965).
- Body weight and body surface area of patients was taken from all patients, and not just those from Region 1, the extra cost of ramucirumab plus best supportive care is $40,718 ($\Delta C_3$), which decreases the estimated incremental cost-effectiveness ratio to $353,532 (from $353,965).
- The probability of hospitalization is based on observed & unadjusted data, the extra cost of ramucirumab plus best supportive care is $40,369 ($\Delta C_4$), which decreases the estimated incremental cost-effectiveness ratio to $350,505 (from $353,965).
- The daily cost of hospitalization is reduced by 25%, the extra cost of ramucirumab plus best supportive care is $38,836 ($\Delta C_5$), which decreases the estimated incremental cost-effectiveness ratio to $337,189 (from $353,965).

- The daily cost of hospitalization is increased by 25%, the extra cost of ramucirumab plus best supportive care is $42,700 ($\Delta C_6$), which increases the estimated incremental cost-effectiveness ratio to $370,741 (from $353,965).

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Eli Lilly, when ramucirumab plus best supportive care is compared with placebo plus best supportive care:

- the extra cost of ramucirumab plus best supportive care is $40,768 (ΔC). Costs considered in the analysis included the cost of the drug, medical resource use costs and other costs associated with treatment.
- the extra clinical effect of ramucirumab plus best supportive care is 0.12 quality-adjusted life years (ΔE). The clinical effect considered in the analysis was based on overall survival, progression-free survival, adverse events and utilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $353,965.

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?

There were two main factors that resulted in a difference in the ICER between the EGP and the submitter. The first was the consideration of all patients in the intention to treat population (ITT) in the best case estimate by the EGP – that is, all patients that were randomized. The submitter had considered only those from Region 1 (Europe, Israel, Australia and the USA) in estimates such as length of stay, and body surface area/weight used to determine drug dosage. The second was the probability of hospitalization of patients. The submitter had constructed a regression model, adjusting for treatment and region. The EGP felt that an unadjusted model, based on observed data for probability of hospitalizations was sufficient.

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

It is difficult to answer this question as patient input was not received from an advocacy group in Canada. pCODR performed a literature search in order to seek out the factors that were most relevant to patients, and it was necessary to include data from outside of Canada. This literature search found that patients did experience some side effects with ramucirumab, though not any more than those experienced with other chemotherapy. Patients also expressed desire for increased survival and better quality of life. All of these factors were considered in the economic analysis.

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

Yes. Though the EGP did not agree with some of the base case inputs, the model was easily manipulated and allowed for many scenario analyses. The provided model was fairly transparent and easy to use.

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?

In the model based on the RAINBOW trial data – ramucirumab plus paclitaxel versus placebo plus paclitaxel – the input that had the greatest effect on the results was the model used for probability of hospitalizations. There was a large difference in the ICER whether it was based on observed, unadjusted data or whether there was a regression model used, adjusting for treatment and region. Length of stay of patients in hospital also had a significant impact on the results. Length of stay using Region 1 data versus using ITT data by treatment region produced very different results.

In the model based on the REGARD trial data – ramucirumab plus best supportive care vs placebo plus best supportive care – the input that had the great effect on the results was the length of stay of patients in hospital. There was a large difference in whether length of stay was for Region 1 patients or for all patients based on the ITT population by treatment arm. Using a different parametric curve to fit the progression-free survival data also impacted the results, but to a lesser degree.

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?

Given the data that is available for this population of patients, yes, the clinical effect and cost estimates provided were adequate. Clinical effect estimates were taken from two clinical trials. However, the comparator of the REGARD trial – best supportive care – is not necessarily supported in clinical practice. Cost estimates were adequate and were taken from appropriate sources.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The BIA model provided was most sensitive to the number of patients eligible for either ramucirumab monotherapy or ramucirumab in combination with paclitaxel, the market share for ramucirumab plus paclitaxel and the cost of ramucirumab.

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

In the main budget impact analysis, wastage was not considered (in contrast to the main cost effective analysis where wastage was considered). The PAG identified wastage as a potential barrier to the implementation of ramucirumab. When wastage is considered in the BIA, the results increase by 5%. The body weight / BSA used in the base case was from only Region 1 patients. A scenario analysis showed that when all patients from all regions are included, the results decrease by 6%.

1.5 Future Research

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

More detail in the pharmacoeconomic evaluation report could be provided explaining the rationale behind the need for a regressions model for the rate of hospitalization.

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

The limitations in the conduct of the clinical research have a direct impact on the economic analysis. The current lack of a standardized approach to second line treatment means that not all potential comparators could be considered directly. While the EGP is satisfied with the analysis and the included comparison with paclitaxel, if future studies include other comparator regimens with ramucirumab, this should be followed by their own economic assessment. The reported potential attenuation of benefit seen in Region 3 (Asia), with its higher level of post-study treatment, suggests more needs to learned about the comparators and sequencing of treatment in this disease. The modest incremental benefit and high incremental cost of ramucirumab suggest that any pricing changes of ramucirumab or its comparators could markedly alter the economic analysis conclusions herein.

2 DETAILED TECHNICAL REPORT – RAM+PAC vs PBO+PAC

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 Gastrointestinal 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 Ramucirumab (Cyramza) for Gastric Cancer. A full assessment of the clinical evidence of Ramucirumab (Cyramza) for Gastric Cancer 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*. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from this publicly available Guidance Report.

This Initial Economic Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report will supersede this 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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