pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Ramucirumab (Cyramza) for Gastric Cancer

October 29, 2015

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	CYRAMZA™ Metastatic Gastric Cancer or Gastro-Esophageal Junction Adenocarcinoma
Role in Review (Submitter and/or	Submitter/Manufacturer
Organization Providing Feedback	Eli Lilly Canada Inc.

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

X	agrees	agrees in part	disagree

Eli Lilly Canada Inc. supports the initial recommendation that there is a net clinical benefit of CYRAMZA™ as therapy for patients with advanced or metastatic gastric cancer or gastro-esophageal junction (GEJ) adenocarcinoma with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and with disease progression following first-line chemotherapy.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

X	Support conversion to final recommendation. Recommendation does not require reconsideration by pERC.	Do not support conversion to final recommendation. Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
4	Initial Economic Guidance Report 1.3 Summary of Economic Guidance Panel Evaluation	Paragraph 1	The comment, *"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."* may imply that the base case parameter for the rate of hospitalization was based on regression modelling. It was noticed that the table referencing the deterministic sensitivity analyses in the CUA report incorrectly indicated that a "negative binomial, adjusted model" was the parameter for probability of hospitalization employed in the base case. However, this was a typographical error made by the manufacturer. The base case parameter for the probability of hospitalization employed in the cost-utility analysis presented for the RAINBOW data was observed data adjusted for treatment and region ("Observed, adjusted Tx Region"). Suggested change: The submitter applied observed rates adjusted for treatment and region for the base case rate of hospitalization input. Regression models were explored but only employed in the sensitivity analysis.

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or ManufacturerProvided Information
8	Initial pERC Recommendation ECONOMIC EVALUATION *Costeffectiveness estimates: Small*	Paragraph 1; Line 5-13	To ensure that the model outcomes were relevant to Canada, we opted to utilize data from Region 1 (North America (US), Europe including Israel, and Australia [n = 398]) because it was thought that treatment practices in these health care systems best reflected the Canadian clinical practice environment. Regional differences were observed across the RAINBOW study population; with respect to patient demographics

	extra benefit and high drug costs impact ICER		(body weight and body surface area [BSA]) and treatment practice (e.g. hospitalization). The costeffectiveness ratio for ramucirumab appears to be highly sensitive to these parameters. **Body weight and BSA** In the RAINBOW study, the body weight and BSA of Region 1 study participants was notably higher than for Region 3 study participants (Table below). **Parameter** / **Value** Body weight: Region 1: 68.15 kg; Region 3: 54.98 kg; All Regions: 63.33 kg Body surface area (BSA): Region 1: 1.78 m^2; Region 3: 1.56 m^2; All Regions: 1.71 m^2 Moreover, a higher average patient weight is commonly used to calculate drug dosages in Canada as the average weight of the North American population has been increasing. For this reason, Region 1 data was deemed to provide the best estimate to calculate the real drug cost of ramucirumab. **Treatment and geographic region** The RAINBOW study data showed that both treatment and geographic region impacted the probability of hospitalization. Rates of hospitalization (table below) were higher among patients receiving PAC (0.036) compared to patients receiving RAM+PAC (0.024; all regions). When accounting for both treatment and region the observed rates across arms increased (0.049 vs 0.032, respectively). **Rate of Hospitalization** (Pre-progression [RAINBOW IPD Analysis]) Rate (per week) Analysis / PAC / RAM+PAC Observed, unadjusted: 0.029 / 0.029 Observed, adjusted Tx: 0.036 / 0.024 Observed, adjusted Tx Region: 0.049 / 0.032

			A consequence of hospitalization is the length of stay. In the RAINBOW study, it was observed that the average length of stay of the ITT population (all regions) receiving PAC was longer (18.20 days) than for those participants receiving RAM+PAC (14.60 days). **Length of Stay** (RAINBOW Safety Population) Cohort — *N* — Days — s.d. All patients — 656 — 16.40 — 1.02
			Region 1 — 393 — 15.20 — 1.12 **RAM+PAC** All patients — 327 — 14.60 — 1.20 Region 1 — 196 — 15.20 — 1.62 **PAC** All patients — 329 — 18.20 — 1.68 Region 1 — 197 — 15.10 — 1.53 However, this difference was less for those participants in Region 1 (15.1 days vs. 15.2 days, respectively). Although the reasons for regional differences in hospital length of stay are not well understood, we felt it was more appropriate to restrict the analysis to Region 1 to ensure that treatment practices most comparable to Canada were employed in the economic analysis. The EGP's re-analysis considered stratification by treatment for the length of hospital stay parameter, but not for the rate of hospitalization. As both parameters impact hospitalization costs, we feel that the same stratification factors should be employed. We would like to better understand the EGP's perspective on this. When treatment stratification is considered for the rates of hospitalization, the resulting ICER may be lower than the EGP's re-analysis.

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.