

pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada’s provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation

This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Ramucirumab (Cyramza)

Submitted Funding Request:

As a single agent or in combination with paclitaxel for the treatment of patients with advanced or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy

Submitted By:
Eli Lilly Canada Inc.

Manufactured By:
Eli Lilly Canada Inc.

NOC Date:
July 16, 2015

Submission Date:
April 15, 2015

Initial Recommendation:
September 3, 2015

Final Recommendation:
October 15, 2015

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding ramucirumab (Cyramza) in combination with paclitaxel, conditional on its cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of 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.

The Committee made this recommendation because it was satisfied that, compared with paclitaxel alone, there is a net clinical benefit with ramucirumab plus paclitaxel based on a clinically meaningful improvement in overall survival, favourable quality of life, manageable toxicities, and an unmet need for more effective therapies in this patient population. In addition, the Committee was satisfied that ramucirumab plus paclitaxel aligns with patient values. However, the Committee noted that ramucirumab plus paclitaxel could not be considered cost-effective at the confidential price, based on the Economic Guidance Panel’s estimates of the range of incremental cost-effectiveness ratios when compared with paclitaxel plus placebo.

pERC does not recommend funding ramucirumab monotherapy for the treatment of patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma with disease progression following first-line chemotherapy as there was considerable uncertainty in the net clinical benefit of ramucirumab monotherapy compared with usual care in the Canadian second-line setting. Although ramucirumab monotherapy offers another treatment option to patients, the modest survival benefit and uncertainty in the generalizability of the results led pERC to conclude that it only partially aligns with patient values. The Committee also concluded that ramucirumab monotherapy was not cost-effective compared with placebo.

**POTENTIAL NEXT STEPS
FOR STAKEHOLDERS**

Pricing Arrangements to Improve Cost-Effectiveness

Given that pERC was satisfied that there is a net clinical benefit of ramucirumab plus paclitaxel in patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma whose disease has progressed following first-line chemotherapy, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness to an acceptable level. However, the Committee noted that a substantial reduction in the price of ramucirumab would likely be required to improve cost-effectiveness.

Frequency of Administration of Paclitaxel

pERC noted that the trial evaluating ramucirumab plus paclitaxel utilized a weekly schedule for administration of paclitaxel. However, some Canadian jurisdictions currently utilize a once every three-weekly schedule for paclitaxel. The Committee noted the likely impact of weekly administration on health systems and patient access, and that provinces may want to investigate the alignment of the administration schedules for paclitaxel and ramucirumab in this patient population in order to limit such impacts.

SUMMARY OF pERC DELIBERATIONS

Gastric cancer and GEJ adenocarcinoma are the ninth and tenth leading causes of cancer-related mortality in men and women, respectively. For patients with advanced or metastatic disease, there is no defined standard of care after failure of first-line chemotherapy, and the intent of such treatment is palliative. pERC noted that for patients with an ECOG performance status of 0 to 2, second-line treatment with a taxane or irinotecan-based chemotherapy provides a modest survival benefit compared with best supportive care. pERC recognized the need for therapies that can improve survival and maintain quality of life in this patient population.

pERC deliberated upon the results of two randomized controlled trials (RAINBOW and REGARD) investigating the use of ramucirumab in patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma after failure of first-line chemotherapy. pERC concluded that there is a net clinical benefit for ramucirumab plus paclitaxel compared with placebo plus paclitaxel (the RAINBOW study). In drawing this conclusion, pERC noted that the overall survival and progression-free survival results were statistically significant and clinically meaningful in favour of ramucirumab plus paclitaxel. Additionally, pERC noted that measures of quality of life were improved for nausea and vomiting and emotional function in favour of ramucirumab plus paclitaxel and were stable for the remaining subscales of the quality of life instruments used in the RAINBOW study. pERC also concluded that there was no worsening of serious toxicities associated with the addition of ramucirumab to treatment with paclitaxel, and that the toxicities observed in the study were expected for an anti-vascular endothelial growth factor (VEGF) treatment.

Upon reconsideration of the Initial Recommendation, pERC acknowledged feedback from the pCODR Provincial Advisory Group (PAG) around the clinical meaningfulness of the magnitude of the overall survival benefit observed in the RAINBOW trial in contrast to similar overall survival benefits observed in other treatments previously reviewed by pCODR in the advanced or metastatic gastrointestinal cancer setting. The Committee reaffirmed its original conclusion that there is a net clinical benefit for ramucirumab plus paclitaxel compared with placebo plus paclitaxel because of the statistically significant absolute difference in overall survival in favour of ramucirumab plus paclitaxel. In particular, the Committee felt that this absolute difference translated to a meaningful relative increase in overall survival in the current context, that is, in patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma.

pERC noted the modest improvement in overall survival in the REGARD trial comparing ramucirumab plus best supportive care to placebo plus best supportive care. However, the Committee considered that in Canada, this patient population (ECOG performance status 0 or 1) would typically receive treatment with chemotherapy; therefore, pERC was not confident that the benefits of ramucirumab monotherapy versus the placebo plus best supportive care comparator in the REGARD trial are generalizable to the Canadian context. pERC noted that there is a subset of patients with intolerance to paclitaxel who may benefit from treatment with ramucirumab monotherapy; however, this specific patient subset was not reported in the REGARD trial and these patients may be eligible for treatment with other chemotherapeutic agents such as irinotecan. Therefore, pERC could not draw a conclusion on the net clinical benefit of ramucirumab monotherapy in patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma due to insufficient evidence.

pERC noted that patient advocacy groups did not provide input on the ramucirumab submission, which challenged the Committee to understand the patient's and caregiver's lived experience with this type of cancer. Consequently, to provide insight for this important component of pERC's deliberations, the Committee discussed a summary of grey literature, compiled by pCODR staff that outlined information on patient experiences and perspectives regarding gastric cancer, GEJ adenocarcinoma, and ramucirumab. pERC concluded that ramucirumab plus paclitaxel aligned with patient values as it provided patients with a treatment option that offered potential for improved overall survival, favourable or maintained quality of life, and a manageable toxicity profile. pERC also noted that although treatment with ramucirumab monotherapy offers an additional treatment option to patients, the modest survival benefit and

[pERC's Deliberative Framework](#) for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

uncertainty in the generalizability of the results for Canadian patients led pERC to conclude that ramucirumab monotherapy was only partially aligned with patient values.

pERC deliberated on the cost-effectiveness of ramucirumab plus paclitaxel compared with paclitaxel plus placebo. pERC concluded that, using the pCODR Economic Guidance Panel's estimates of the incremental cost-effectiveness of treatment with ramucirumab plus paclitaxel was not cost-effective at the submitted confidential prices compared with paclitaxel plus placebo. pERC noted that the high estimates of the incremental cost-effectiveness were largely due to the small gain in clinical effectiveness and the high cost of ramucirumab. Similarly, pERC also concluded that ramucirumab monotherapy compared to best supportive care was not cost-effective. pERC noted that in order to improve cost-effectiveness to an acceptable level in either analysis, a substantial reduction in the price of ramucirumab would be required.

Upon reconsideration of the Initial Recommendation, pERC acknowledged feedback from the manufacturer of ramucirumab regarding the inputs used in the submitted economic model and noted that the Economic Guidance Panel revised their report accordingly. The Committee reaffirmed that it agreed with the approach used by the Economic Guidance Panel, which was based on the opinion of the Clinical Guidance Panel, to arrive at its estimates of the incremental cost-effectiveness of ramucirumab plus paclitaxel compared with placebo plus paclitaxel.

pERC discussed the feasibility of implementing a funding recommendation for ramucirumab plus paclitaxel. The Committee noted the small number of patients expected to be eligible for second-line treatment, which would prevent vial sharing of unused portions of reconstituted drug. While drug wastage was included in both cost-utility analyses, it was not considered in the Submitter's base case budget impact analysis. When the EGP included wastage in its re-analysis of the budget impact, the budget impact increased by 5%. Additionally, pERC considered that some Canadian jurisdictions administer paclitaxel once every three weeks rather than once weekly, as in the RAINBOW trial. The Committee noted the likely impact of a weekly administration schedule for paclitaxel on health systems and on patient access as a potential barrier to implementation as patients would be required to travel more frequently to receive treatment compared with a once every three-weekly schedule. Additionally, a change in the administration schedule of paclitaxel from that used in the RAINBOW trial to once every three weeks would result in misalignment of the administration schedules of paclitaxel and ramucirumab.

Upon reconsideration of the Initial Recommendation, pERC acknowledged feedback from the PAG that there is variation across the provinces in the standard of care for patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma and that there may be an increase in cost due to weekly administration of paclitaxel rather than the three-weekly schedule currently used in some jurisdictions. The Committee supported its original recommendation regarding ramucirumab plus paclitaxel in this disease setting and noted that the increased costs of weekly paclitaxel administration would likely have only a very small impact on the incremental cost-effectiveness ratio.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from pCODR's Provincial Advisory Group.

Patient advocacy group input was not received for this review; however, pERC used a summary provided by pCODR through a comprehensive search of published and grey literature on patient experiences and perspectives regarding gastric cancer and GEJ adenocarcinoma and ramucirumab to inform its deliberations.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- the Submitter (Eli Lilly Canada Inc.)

The pERC initial recommendation was to fund ramucirumab, conditional on the cost-effectiveness being improved to an acceptable level, when used in combination with paclitaxel for the treatment of patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma with ECOG performance status of 0 or 1 and with disease progression following first-line chemotherapy.

Feedback on the pERC Initial Recommendation indicated that the manufacturer and pCODR's Provincial Advisory Group agreed with the initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review was to evaluate the safety and efficacy of ramucirumab, as monotherapy and as part of combination therapy, for the treatment of patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma after prior chemotherapy.

Studies included: Two RCTs in patients previously treated with chemotherapy

The pCODR systematic review included two randomized trials, RAINBOW and REGARD. Both RAINBOW (n=665) and REGARD (n=355) were double-blind, multi-national, parallel-arm, placebo-controlled trials. RAINBOW randomized patients 1:1 to treatment with ramucirumab plus paclitaxel or to placebo plus paclitaxel. REGARD randomized patients 2:1 to treatment with ramucirumab plus best supportive care or to placebo plus best supportive care. Crossover was not permitted in either trial.

The pCODR review was also provided contextual information from a manufacturer-submitted network meta-analysis (NMA) of ramucirumab and paclitaxel combination therapy versus other second-line treatments for adult patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma.

Patient populations: ECOG performance status 0 or 1.

Both trials included patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma who had previously received chemotherapy. Both trials included patients with ECOG performance status of 0 or 1. In RAINBOW, patients were predominantly white (61%), 71% were male, 61% had an ECOG performance status of 1, and the median age was 61 years.

In REGARD, patients were also predominantly white (77%), 70% were male, 72% had an ECOG performance status of 1, and the median age was 60 years. pERC noted that baseline differences between treatment arms may have existed in the number of metastatic sites (≥ 3 ; ramucirumab, 32%; placebo, 39%), progression-free interval after previous treatment (≥ 6 months; ramucirumab, 34%; placebo, 29%), and presence of peritoneal metastases (ramucirumab, 27%; placebo, 38%), all of which may have biased the results in favour of ramucirumab monotherapy.

Key efficacy results: Improvement in overall survival for ramucirumab plus paclitaxel

In the RAINBOW trial, pERC noted a statistically significant and clinically meaningful improvement in overall survival in the context of advanced gastric cancer following failure of first-line chemotherapy in favour of ramucirumab plus paclitaxel. Median overall survival was 9.6 months in the ramucirumab plus paclitaxel arm compared with a median of 7.4 months in the placebo plus paclitaxel arm; hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.68 to 0.96; $p < 0.017$. The estimated OS at six months was 72% in the ramucirumab plus paclitaxel group and 57% in the placebo plus paclitaxel group; one-year OS rates were 40% and 30%. The Committee also noted a statistically significant and likely clinically meaningful improvement in median progression-free survival for the ramucirumab plus paclitaxel arm compared with the placebo plus paclitaxel arm (median 4.4 months versus [vs.] 2.9 months); HR 0.64, 95% CI 0.54 to 0.75; $p < 0.0001$.

Upon reconsideration of the Initial Recommendation, pERC acknowledged feedback from the pCODR Provincial Advisory Group (PAG) around the clinical meaningfulness of the magnitude of the overall survival benefit observed in the RAINBOW trial in contrast to similar overall survival benefits observed in other treatments previously reviewed by pCODR in the advanced or metastatic gastrointestinal cancer setting. The Committee reaffirmed its original conclusion that there is a net clinical benefit for ramucirumab plus paclitaxel compared with placebo plus paclitaxel. The Committee felt that the absolute difference in OS of 2.2 months in favour of ramucirumab plus paclitaxel represented a clinically meaningful difference, as the expected overall survival in patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma is generally less than one year, while patients with other advanced or metastatic gastrointestinal cancers generally have longer expected survival.

pERC noted that, with respect to the REGARD trial, overall survival was statistically significantly improved in favour of ramucirumab (median 5.2 months) compared with placebo (median 3.8 months); HR 0.78, 95% CI 0.60 to 1.0; $p < 0.047$. The estimated OS at six months was 41.8% in the ramucirumab plus best supportive care group and 31.6% in the placebo plus best supportive care group; one-year OS rates were 17.6% and 11.8%. Median progression-free survival was also statistically significantly longer in the ramucirumab arm compared with the placebo arm (median 2.1 months vs. 1.3 months); HR 0.48, 95% CI 0.38 to 0.62; $p < 0.0001$. pERC discussed the clinical significance of the increase in overall survival observed with ramucirumab monotherapy and differing opinions were debated. pERC noted the Clinical Guidance Panel's conclusion that there may be a net clinical benefit with the use of ramucirumab monotherapy in patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma with an ECOG performance status of 0 or 1. However, the Committee concluded that, at best, the difference in overall survival represented a very modest benefit. Additionally, there was uncertainty in this estimate due to questions surrounding the generalizability of the REGARD trial results to the Canadian context as the patient population in the trial (ECOG performance status 0 or 1) would typically receive treatment with chemotherapy.

Quality of life: Improvement in some subscales and overall maintenance in quality of life with ramucirumab plus paclitaxel

pERC noted that in the RAINBOW trial, health-related quality of life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer Questionnaire (EORTC-QLQ-C30) and the European Quality of Life Questionnaire-5 Dimension (EQ-5D) Index Score. pERC noted that significant differences in time to deterioration in the emotional functioning (HR 0.64; 95% CI 0.49 to 0.84) and the nausea and vomiting (HR 0.75; 95% CI 0.57 to 0.97) scales of the EORTC-QLQ-C30 were reported in favour of the ramucirumab plus paclitaxel arm and in the diarrhea symptom scale in favour of the paclitaxel plus placebo arm. No statistically significant differences in the remaining scales were noted between treatment groups. pERC concluded that the significant differences in the nausea and vomiting symptom scale in favour of the ramucirumab plus paclitaxel arm were clinically meaningful given that nausea and vomiting are a common disease-related symptom in these patients and that treatment with ramucirumab plus paclitaxel may delay the onset of these disease-related symptoms compared with paclitaxel alone. The Committee considered that the significant difference in the emotional function scale was also clinically meaningful.

pERC discussed that, although HRQoL was measured in the REGARD trial using the EORTC-QLQ-C30, there was a lack of post-baseline data for the majority of patients in the trial. Therefore, no data on time-to-deterioration were available for pERC deliberations.

Safety: Expected VEGF inhibitor toxicities such as hypertension

pERC noted that in the RAINBOW trial, 99.1% of patients in the ramucirumab plus paclitaxel group experienced an adverse event compared with 97.9% of patients in the placebo plus paclitaxel group. In the REGARD trial, 94.5% of patients who received ramucirumab experienced an adverse event compared with 87.8% of patients who received placebo. In both trials, the proportion of patients who experienced a serious adverse event was similar between the group of patients who received ramucirumab compared with those who received placebo (RAINBOW, 46.8% vs. 42.2%; REGARD, 44.9% vs. 44.3%). Grade 3 or higher adverse events occurred in more patients in the ramucirumab plus paclitaxel group (81.7%) than in the placebo plus paclitaxel group (62.6%) in the RAINBOW trial, whereas they occurred in a similar proportion of patients in both treatment groups in the REGARD trial (ramucirumab, 56.8%; placebo, 58.3%). Grade 3 or 4 adverse events more commonly occurring in patients treated with ramucirumab and paclitaxel in the RAINBOW trial included neutropenia, hypertension, and fatigue. In the REGARD trial, grade 3 or 4 hypertension and abdominal pain were more commonly reported in patients who received ramucirumab. pERC noted that the toxicities of treatment with ramucirumab, as a VEGF inhibitor, were both expected and manageable.

Comparator information: No consistent standard of care in Canada

pERC noted that, in Canada, there is no defined standard of care for patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma after failure of first-line therapy. In patients with an ECOG performance status of 0 to 2, taxanes or irinotecan-based chemotherapy are commonly used in Canadian practice.

pERC also noted that in the REGARD trial, the use of placebo plus best supportive care for patients with an ECOG performance status of 0 or 1 is not reflective of Canadian practice as these patients would be considered candidates for chemotherapy.

Limitations: Trials conducted in patients with ECOG performance status of 0 or 1

pERC noted that the exclusion of patients with an ECOG performance status of 2 or higher was a potential limitation of both studies; therefore, pERC was unable to comment on patients with ECOG performance status of 2 or higher, a patient population with a need for more effective therapies.

In the REGARD trial, pERC noted that the choice of best supportive care as the comparator was inappropriate for the Canadian context as fit patients (ECOG performance status 0 or 1) would generally receive chemotherapy after failure of first-line chemotherapy. pERC also noted that the baseline imbalances between the treatment groups in the REGARD trial may have favoured the ramucirumab alone arm. Additionally, due to problems with accrual, the final sample size was modified several times and was approximately half that originally planned. Although the study reported a power of 80%, it was likely to be less due to the smaller than anticipated difference in overall survival observed between treatment groups, thus increasing the uncertainty around the estimate.

Need: Few options, patients need more effective treatments

pERC noted that first-line treatment of advanced or metastatic gastric cancer or GEJ adenocarcinoma includes chemotherapy, typically with a fluoropyrimidine and a platinum. After failure of first-line therapy in patients who maintain an ECOG performance status of 0 to 2, the Committee noted that, based on the opinion of the Clinical Guidance Panel, treatment with taxanes (docetaxel, paclitaxel) and irinotecan-based chemotherapy has demonstrated modest improvements in survival when compared with best supportive care (i.e., difference in median overall survival up to 1.6 months); however, there remains a large unmet need for more effective therapies.

PATIENT-BASED VALUES

Values of patients with gastric cancer or GEJ adenocarcinoma: Prolongation of survival, improved quality of life, and reduction of toxicities

pERC noted that no patient advocacy groups provided input on the review of ramucirumab. The Committee discussed a summary of grey literature which illustrated patient experiences and perspectives on gastric cancer, GEJ adenocarcinoma and ramucirumab.

pERC noted that the summary suggested that patients with gastric cancer or adenocarcinoma value treatments that offer a longer remission, prolongation of life, and improved quality of life, with fewer side effects. Patients with gastric cancer or GEJ adenocarcinoma experience dysphagia, choking, and pain on swallowing that makes eating difficult and leads to poor nutrition and an inability to maintain their weight. Patients also experience fatigue and weakness. Helping patients manage these symptoms was extremely distressing for patients' caregivers. pERC noted the reported large emotional and financial impact on the lives of caregivers of patients with gastric cancer.

Patient values on treatment: Willingness to tolerate side effects for improved outcomes

Five patients were identified in the search who had experience receiving treatment with ramucirumab. The Committee noted that the summary suggested that some patients who have received treatment with ramucirumab experienced favourable outcomes while some patients reported the opposite. Patients reported experiencing side effects of treatment with ramucirumab (e.g., fatigue, hypertension), but some patients appeared willing to tolerate those side effects for prolonged survival and improvements in symptoms of their disease and overall quality of life.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis

The pCODR Economic Guidance Panel assessed two cost-utility analyses in patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma after prior chemotherapy and ECOG performance status of 0 or 1: ramucirumab plus paclitaxel compared to placebo plus paclitaxel (based on RAINBOW), and; ramucirumab plus best supportive care compared to placebo plus best supportive care (based on REGARD). Both were partitioned survival models with three health states: pre-progression, post-progression, and death.

Basis of the economic model: Clinical and economic inputs

Costs considered in the models included drug (ramucirumab, paclitaxel) acquisition and administration, best supportive care, third-line treatments, follow-up care, hospitalization, and end-of-life care. Clinical inputs included progression-free survival, overall survival, time on treatment, treatment-related adverse events, health state utilities, disutilities, and response-specific utilities. Health state utilities in both models were based on utility data collected in the RAINBOW study.

Drug costs: confidential price, comparator likely costs less

At the list price, ramucirumab costs \$909.42 per 100 mg vial or \$4547.10 per 500 mg vial. At the recommended dose of 8 mg/kg every 2 weeks and assuming an average weight of 70 kg, the cost per day is \$363.77 and \$10,185.50 per 28-day course. At the submitted confidential price, ramucirumab costs \$■■■■ per 100 mg vial or \$■■■■ per 500 mg 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.*)

At the submitted price, 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. At the recommended dose of 80 mg/m² on days 1, 8 and 15 of a 28-day cycle and assuming an average body surface area of 1.7 m², the cost per day is \$4.84 and \$135.46 per 28-day course. The EGP noted that the price of paclitaxel may be quite significantly lower in Canadian jurisdictions than that used in the Submitter's model.

Cost-effectiveness estimates: Small extra benefit and high drug costs impact ICER

pERC noted that the inputs that had the largest impact on the incremental cost-effectiveness ratio, in both cost-utility analyses were the drug cost, in addition to the length of stay in hospital, body weight and body surface area estimates, probability of hospitalization, and the daily cost of hospitalization. The choice of

parametric function to model progression-free survival had an impact on the results in the REGARD-based analysis. pERC agreed with the approach taken by the EGP to use the data from all patients in the RAINBOW trial to inform the inputs for the length of stay, body weight and body surface area as the data from all patients would provide better estimates. pERC also agreed with the EGP's approach to use the observed and unadjusted data on the probability of hospitalization from the RAINBOW trial and with the decision to account for uncertainty in the daily cost of hospitalizations through a 25% increase and decrease. Lastly, the Committee agreed with the Economic Guidance Panel's approach to use a Weibull distribution to fit the progression-free survival data in the REGARD-based model as it better modeled the survival that would be expected in clinical practice, a recommendation supported by the Clinical Guidance Panel. Wastage was included in both cost-utility analyses. pERC accepted the EGP's reanalysis estimates adjusting for these factors, which were higher than the Submitter's base case estimates for both analyses, and concluded that ramucirumab plus paclitaxel and ramucirumab plus best supportive care could not be considered cost-effective at the confidential price for ramucirumab. pERC noted that in order to reduce the incremental cost-effectiveness to an acceptable level, a substantial reduction in the price of ramucirumab would be required.

Upon reconsideration of the Initial Recommendation, pERC acknowledged feedback from the manufacturer of ramucirumab regarding the inputs used in the submitted economic model and noted that the Economic Guidance Panel revised their report accordingly. The Committee reaffirmed that it agreed with the approach used by the Economic Guidance Panel, which was based on the opinion of the Clinical Guidance Panel, to arrive at its estimates of the incremental cost-effectiveness of ramucirumab plus paclitaxel compared with placebo plus paclitaxel.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: frequency of paclitaxel administration

pERC discussed factors affecting the feasibility of implementing a funding recommendation for ramucirumab monotherapy or ramucirumab plus paclitaxel in patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma who have received prior chemotherapy.

pERC noted that the Provincial Advisory Group expressed concerns with drug wastage as a potential barrier to implementation. The Committee considered the small number of patients expected to be eligible for second-line treatment, which would prevent vial sharing of unused portions of reconstituted drug and noted that the Submitter did not include wastage in the budget impact analysis. When the EGP incorporated wastage in its re-analysis, the budget impact increased by 5%.

pERC also noted that the Provincial Advisory Group expressed concern with the additional costs of administering paclitaxel as a potential barrier to implementation. Some Canadian jurisdictions do not currently fund paclitaxel for gastric cancer, and some others that do administer paclitaxel once every three weeks rather than once weekly, as in the RAINBOW trial. The Committee noted the likely impact of a weekly administration schedule for paclitaxel on health systems and on patient access as a potential barrier to implementation as patients would have to travel more frequently to receive treatment compared with a once every three weeks schedule. Additionally, any changes to the administration schedules of paclitaxel and ramucirumab would have to keep their cycle lengths in harmony.

Upon reconsideration of the Initial Recommendation, pERC acknowledged feedback from the PAG that there is variation across the provinces in the standard of care for patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma and that there may be an increase in cost due to weekly administration of paclitaxel rather than the three-weekly schedule currently used in some jurisdictions. The Committee supported its original recommendation regarding ramucirumab plus paclitaxel in this disease setting and noted that the increased costs of weekly paclitaxel administration would likely have only a very small impact on the incremental cost-effectiveness ratio.

DRUG AND CONDITION INFORMATION

Drug Information	<ul style="list-style-type: none"> Human monoclonal antibody (IgG1) 100mg & 500mg vials Recommended dosage of 8 mg/kg administered intravenously every two weeks as a single agent on days 1 and 15 of a 28 day cycle prior to paclitaxel administered intravenously on days 1, 8, and 15 of a 28 day cycle
Cancer Treated	<ul style="list-style-type: none"> Metastatic Gastric Cancer or Gastro-Esophageal Junction Adenocarcinoma
Burden of Illness	<ul style="list-style-type: none"> Stomach cancers (gastric and GEJ) are the 9th and 10th leading causes of cancer-related mortality in men and women, respectively Estimated 4,400 new cases of esophago-gastric adenocarcinoma, two-thirds (or approximately 3,000) are expected to present with advanced, unresectable disease
Current Standard Treatment	<ul style="list-style-type: none"> No defined standard of care for patients after failure of first-line therapy
Limitations of Current Therapy	<ul style="list-style-type: none"> Current options which include taxanes (docetaxel, paclitaxel) and irinotecan-based chemotherapy have demonstrated modest improvements in survival when compared with best supportive care

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

pERC Membership During Deliberation of the Initial Recommendation

Dr. Anthony Fields, Oncologist (Chair)
 Dr. Maureen Trudeau, Oncologist (Vice-Chair)
 Dr. Scott Berry, Oncologist
 Bryson Brown, Patient Member
 Dr. Matthew Cheung, Oncologist
 Mario de Lemos, Pharmacist
 Dr. Sunil Desai, Oncologist
 Mike Doyle, Economist

Dr. Bill Evans, Oncologist
 Dr. Allan Grill, Family Physician
 Dr. Paul Hoskins, Oncologist
 Danica Wasney, Pharmacist
 Carole McMahon, Patient Member Alternate
 Jo Nanson, Patient Member
 Dr. Tallal Younis, Oncologist
 Dr. Kelvin Chan, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Dr. Scott Berry, Mario de Lemos & Dr. Maureen Trudeau who were not present for the meeting
- Dr. Bill Evans, who was excluded from deliberations and voting due to a conflict of interest
- Jo Nanson, who was the designated non-voting patient member alternate for this meeting

pERC Membership During Deliberation of the Final Recommendation

Dr. Anthony Fields, Oncologist (Chair)	Dr. Paul Hoskins, Oncologist
Dr. Maureen Trudeau, Oncologist (Vice-Chair)	Don Husereau, Health Economist
Dr. Scott Berry, Oncologist	Dr. Anil Abraham Joy, Oncologist
Bryson Brown, Patient Member	Karen MacCurdy-Thompson, Pharmacist
Dr. Kelvin Chan, Oncologist	Carole McMahon, Patient Member Alternate
Dr. Matthew Cheung, Oncologist	Dr. Catherine Moltzan, Oncologist
Dr. Craig Earle, Oncologist	Jo Nanson, Patient Member
Dr. Allan Grill, Family Physician	Danica Wasney, Pharmacist

All members participated in deliberations and voting on the final recommendation except:

- Jo Nanson, who was the designated non-voting patient member alternate for this meeting
- Dr. Anil Abraham Joy, who was in an observing (non-voting) capacity for orientation to pERC

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of ramucirumab (Cyramza) for metastatic gastric cancer or gastro-esophageal junction adenocarcinoma, through their declarations, two members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines* and one of these members was excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Eli Lilly Canada Inc., as the primary data owner, did not agree to the disclosure of economic information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

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