Cost-effectiveness of ramucirumab (Cyramza®) for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression following previous treatment with chemotherapy.

The NCPE has issued a recommendation regarding the cost effectiveness of ramucirumab (Cyramza®). Following NCPE assessment of the applicant's submission, ramucirumab (Cyramza®) is not considered cost effective for the treatment of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma and therefore is not recommended for reimbursement.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Eli Lilly and Company Limited) economic dossier on the cost effectiveness of ramucirumab (Cyramza®). The NCPE uses a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **July 2016**

Summary

Background

- In December 2015, Eli Lilly and Company Limited submitted a dossier in support of the clinical and cost effectiveness of ramucirumab (Cyramza®). Specifically, the dossier related to the use of ramucirumab for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior chemotherapy.
- Ramucirumab is to be administered as a hospital infusion in the out-patient care setting with dosing according to body weight. The goal of ramucirumab treatment within gastric or gastro-oesophageal cancer is to delay progression and improve survival through the mechanism of angiogenesis inhibition.
- Ramucirumab is intended to be given in combination with paclitaxel in such patients who have previously received platinum and fluoropyrimidine chemotherapy. Ramucirumab is licensed as monotherapy in patients who have received either prior platinum or fluoropyrimidine chemotherapy and for whom treatment in combination with paclitaxel would not be appropriate.

1. Comparative effectiveness of ramucirumab

- The clinical efficacy data for ramucirumab was drawn from two pivotal randomised clinical trials, RAINBOW and REGARD, which examined ramucirumab in combination with paclitaxel, and as monotherapy, respectively.
- RAINBOW included 665 adults randomised in a 1:1 ratio to either ramucirumab or placebo once every two weeks, with both arms receiving conventional paclitaxel treatment on weeks 1,2 and 3 of each four-week cycle. REGARD included 355 adults randomised in a 2:1 ratio to receive either ramucirumab or placebo once every two weeks. Patients included in both trials were required to have an ECOG score of 0 or 1. The primary endpoint in both trials was overall survival (OS); progression-free survival (PFS) and health-related quality of life (HRQoL) were examined among other secondary endpoints.
- Median OS in RAINBOW was found to be 9.6 months in the ramucirumab arm versus 7.4 months in the placebo arm (equating to a 2.3 month improvement, HR=0.81,

95% CI 0.68-0.96, p=0.02). Median OS in REGARD was found to be 5.2 months in the ramucirumab arm versus 3.8 months in the placebo arm, equating to a 1.4 month improvement (HR=0.78, 95%CI 0.6-1.0, p=0.05).

- Statistically significant improvements in PFS were observed with ramucirumab treatment in RAINBOW (median PFS difference=1.5 months, p<0.01) and REGARD (median PFS difference=0.8 month, p<0.01). HRQoL results suggested a trend towards favouring treatment with ramucirumab, though overall results were not statistically significant for either combination therapy or monotherapy.
- A network meta-analysis (NMA) was performed by the applicant in order to compare ramucirumab combination therapy to docetaxel or irinotecan, the latter treatments representing alternative chemotherapy options in the second-line gastric cancer setting. For overall survival, ramucirumab combination therapy was found to have a survival advantage versus irinotecan (HR 1.39, 95% CrI 1.01-1.92) and BSC (HR 2.94, 95% CrI 1.41-5.88). No statistically significant improvement was observed versus docetaxel. The results of the NMA require cautious interpretation as the studies included were highly heterogeneous.

2. Safety of ramucirumab

- Results of the RAINBOW trial found that for combination therapy, the incidence of grade 3 or 4 adverse drug reactions was higher for patients in the ramucirumab arm (42.5% versus 37.1%). Adverse drug events of grade 3 or higher which occurred more frequently in the ramucirumab arm included neutropenia (40.3% versus 18.8%), leukopenia (17.4% versus 6.7%), hypertension (14.7% versus 2.7%) and fatigue (11.9% versus 5.0%). The proportion of adverse drug events leading to treatment discontinuation and the proportion of treatment-related deaths were similar between the two trial arms.
- Within the REGARD trial, adverse drug events of grade 3 or higher which occurred more frequently in the ramucirumab arm included hypertension (7.6% versus 2.6%) and abdominal pain (5.9% versus 2.6%). While the overall incidence of grade 3 or higher adverse events was higher in the ramucirumab arm, the difference was nonetheless small and the proportion of treatment-related deaths was similar

among the trial arms.

- Overall, results of the phase III trials of ramucirumab indicated that the drug has an acceptable tolerability profile in the context of advanced gastric or gastro-oesophageal cancer.

3. Cost effectiveness of ramucirumab

Methods

- Eli Lilly and Company Limited submitted a global model of cost effectiveness which had been adapted to the Irish context. This comprised a cost utility model for each of ramucirumab combination therapy and monotherapy.
- Ramucirumab combined with paclitaxel was compared to paclitaxel alone, and also to docetaxel and irinotecan, which represent alternative chemotherapy options in the second-line gastric cancer setting. Ramucirumab monotherapy was considered to be reserved for patients who cannot tolerate chemotherapy and as such was compared only to best supportive care.
- Each model took the form of a partitioned survival model with three health states: pre-progression, post-progression and death. The models adopted a lifetime time horizon equating to 7.23 years and a cycle length of one week, with discounting of costs and utilities at a rate of 5% per annum. The analyses were presented from the perspective of the HSE with only direct healthcare costs being considered.
- Patients enter the model at the point of initiation of second-line treatment/BSC and remain in this state while they have stable disease or partial or complete response, continuing to receive active treatment until disease progression or treatment discontinuation. Following progression, patients transition to the post-progression state. Patients may enter the death state from either the pre-progression or post-progression state.
- Clinical outcome data (PFS and OS) were incorporated into the models using survival distributions based on the overall RAINBOW and REGARD trial populations (ramucirumab combination therapy and monotherapy, respectively). For the comparators within the combination therapy model, PFS and OS data were incorporated using hazard ratios (versus ramucirumab) which were obtained from

the network meta-analysis (see section 1) and applied to the ramucirumab survival distributions. The RG noted that there was a lack of consistency in the approaches used for modelling survival between the combination and monotherapy models, and questioned some aspects of the methodology applied.

- Health benefit was expressed as quality adjusted life years (QALYs). Utility values for the pre-progression and post-progression health states were derived from the RAINBOW trial.
- The impact of adverse events was incorporated using a QALY decrement for each adverse event type identified as important (grade 3 or 4, occurring in >5% patients, and expected to have impact on costs and QALYs) within the ramucirumab pivotal trials. Event durations and utility values were sourced from a NICE appraisal of a drug used to treat lymphoma (due to failure to obtain a suitable source within the disease area of gastric cancer).
- The following costs were included in the models: provision of second-line and third-line drug therapy (including drug acquisition, drug administration and pre-medication), best supportive care, adverse events costs, follow-up care and hospitalisations.
- Drug costs were calculated per model cycle based on published drug regimens, body weight, body surface area (BSA), duration of treatment, and relative dose intensity as per clinical trials. Following NCPE recommendation, body weight and BSA values were taken from the 'Region 1' population within the ramucirumab pivotal trials (included Europe, Israel, Australia and the USA and therefore more likely to resemble Irish population values than the overall trial population).

Results

- Relative to its nearest comparator, paclitaxel, ramucirumab combination therapy resulted in an ICER of €391,611 per QALY, representing incremental gains of 0.1 life year and 0.1 QALY at an incremental cost of €35,245.
- For ramucirumab monotherapy, the ICER relative to BSC was €252,719 per QALY, representing an incremental gain of 0.1 QALY at an incremental cost of €29,700.
- For both models, the high acquisition cost of ramucirumab accounted for the

majority of the incremental costs.

Sensitivity analysis

- Probabilistic sensitivity analyses found a 0% probability of cost effectiveness for either combination or monotherapy treatment at the conventional willingness-to-pay threshold of €45,000 per QALY.
- Deterministic sensitivity analyses found that the results were affected by changes in the distributions used for modelling the survival inputs, and by changes in the rate of hospitalisation or associated duration of stay. However, the RG was of the opinion that the influence of these changes is minimal in the context of the overall modest survival gains associated with ramucirumab and the very high proposed drug acquisition cost, these factors being the overwhelming drivers of the model results.

4. Budget impact of ramucirumab

- The budget impact analysis provided by the applicant combined the results for combination therapy and monotherapy ramucirumab. The analysis projected that the number of patients likely to receive ramucirumab would increase from 25 in 2016 to 104 in 2020.
- Acquisition costs associated with ramucirumab, given the above patient numbers, would rise from €0.8 million to €3.4million, resulting in a 5-year total acquisition cost of €11.5 million.
- The corresponding administration costs would rise from €0.08 million to €0.35 million, resulting in a 5-year total administration cost of €1.2 million.
- Gross budget impact figures were not significantly altered by accounting for drug costs averted due to switching of treatments.

5. Conclusion

Given the modest QALY gain associated with ramucirumab treatment and the very high corresponding drug costs, the NCPE considers ramucirumab not to be cost effective as either combination therapy with paclitaxel or as monotherapy, and therefore cannot recommend this drug for reimbursement at the submitted price.