

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125477Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo for Regulatory Action

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| Date | Electronic stamp date |
| From | Richard Pazdur, MD |
| Subject | Office Director Decisional Memo |
| BLA # | STN BL 125477 |
| Applicant Name | Eli Lilly and Company |
| Date of Submission | March 27, 2013 (received) |
| PDUFA Goal Date | April 23, 2014 |
| Proprietary Name / Established (USAN) Name | Cyramza Injection\ Ramucirumab |
| Dosage Forms / Strength | Injection for intravenous infusion/ 100 (10mg/mL) and 500 mg (10 mg/mL) |
| Proposed Indication(s) | Cyramza, as a single-agent, is indicated for the treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy |
| Recommended Action for NME: | <i>Approval</i> |

| Material Reviewed/Consulted | Names of discipline reviewers |
|------------------------------------|--------------------------------------|
| OND Action Package, including: | |
| Division Director | Patricia Keegan |
| Regulatory Project Manager Review | Sharon Sickafuse |
| Medical Officer Review | Sandra J Casak |
| Statistical Review | Hui Zhang |
| Pharmacology Toxicology Review | Gabriel S. Khasar |
| Quality Review (OBP) | Michele K. Dougherty |
| Microbiology Review | Kalavati C Suvarna |
| Microbiology Review | Candace Gomez-Broughton |
| Clinical Pharmacology Review | Lillian H Zhang |
| OSI | Lauren Iacono-Connors |
| CDTL Review | Steven Lemery |
| OSE/DMEPA | Jibril Abdus-Samad |
| OSE/DRISK | Cynthia LaCivita |
| QT IRT Consult Review | Dhananjay D Marathe |
| OPDP | Quynh-Van Tran |

OND=Office of New Drugs
 OBP=Office of Biologic Products
 OPDP=Office of Prescription Drug Promotion
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 OSI=Office of Scientific Investigations
 DRISK=Division of Risk Management
 CDTL=Cross-Discipline Team Leader
 QT IRT=Interdisciplinary Review Team

1. Introduction and Background

On August 23, 2013, Eli Lilly and Company submitted the last portion of its rolling review submission for Cyramza (ramucirumab), which is a recombinant human IgG1 kappa monoclonal antibody that binds to the extracellular domain of the human vascular endothelial growth factor receptor-2 (VEGFR-2). Ramucirumab effectively blocks the interaction of VEGFR-2 with its ligands, VEGF-A, VEGF-C, and VEGF-D, resulting in inhibition of VEGF-stimulated activation of both VEGFR-2 and downstream signaling pathways.

Adenocarcinoma of the stomach and gastro-esophageal junction is the seventeenth most common malignancy in the United States. According to the National Cancer Institute, there will be an anticipated 21,600 new cases of gastric cancer and 10,990 deaths due to gastric cancer in 2013. The median age at diagnosis is 69 years of age, with a male predominance (2:1) and a higher incidence in non-Whites (Black, Hispanic, Native Americans) than in non-Hispanic Whites.

Data obtained since 2005, indicate 5-year survival rates of 25%, supporting the need for more effective treatments. Drugs which carry an FDA-approved indication for treatment of metastatic gastric cancer are doxorubicin, docetaxel, mitomycin C, fluorouracil, and trastuzumab; however doxorubicin and mitomycin C are no longer commonly used for treatment of gastric cancer. As summarized in the NCCN Clinical Practice Guidelines, current recommendations for advanced, localized gastric cancer/gastro-esophageal junction cancer consists of multi-modality approaches of surgery, pre-or post-operative chemotherapy, with or without radiotherapy. Treatment of metastatic disease consists of two- or three-drug combination chemotherapy regimens; common regimens include fluoropyrimidine and platinum, with or without epirubicin or docetaxel. Current recommendations for second-line therapy include single agent taxane, irinotecan alone or in combination with a taxane, fluoropyrimidines, or platinum; trastuzumab is indicated for patients with HER-2 overexpressing tumors.

2. CMC

The CMC discipline has provided an overall acceptability recommendation for the manufacturing of the drug product and substance and there are no issues that preclude approval. Stability testing supports an expiry of the drug product of (b) (4) from the date of manufacture when stored at 2-8°C.

Ramucirumab is a recombinant, human, immunoglobulin IgG1, kappa monoclonal antibody that binds to VEGFR-2.

(b) (4) It is manufactured in accordance with GMP to yield a pure and potent product. Ramucirumab injection is supplied in 100 mg and 500 mg single-dose vial strengths in a sterile, preservative-free liquid solution at concentration of 10 mg/ml.

The immunogenicity assays were determined to be sensitive and reliable for the detection of both binding and neutralizing anti-drug antibodies in the absence of excess drug. However, since there was insufficient data in the BLA to demonstrate the anti-drug antibody assay was capable of detecting antibodies against ramucirumab at levels of drug expected to be present in serum samples at the time of collection (drug tolerance), two post-marketing requirements have been identified.

3. Nonclinical Pharmacology/Toxicology

There are no outstanding nonclinical issues that preclude approval. The BLA contained the results of pharmacodynamic studies, short-term and long-term toxicology studies in non-human primates, and toxicology studies to assess effects on wound healing. Assessment of carcinogenicity and genetic toxicology studies were not required to support the BLA, because the indicated patient population has a median survival of less than 6 months with ramucirumab treatment. Reproductive toxicology studies were not required to support the BLA based on published literature demonstrating the critical role of this pathway in embryo-fetal development. Therefore, product labeling will indicate that ramucirumab, which inhibits this pathway, has embryofetal toxicity in humans.

In vitro pharmacology studies demonstrated that ramucirumab binds specifically to the human VEGFR2 receptor but not the murine homolog. Upon binding to VEGFR2, ramucirumab inhibits VEGF ligand binding to its receptor, thus resulting in inhibition of ligand-induced phosphorylation of the VEGFR2 receptor. In addition, ramucirumab inhibited VEGF-induced proliferation and migration of human cells in a murine-human xenograft model.

Short (1-month) and chronic (39-week) toxicology studies were conducted in cynomolgus monkeys. Findings included effects on bone growth, renal toxicity, hemorrhage, cardiac toxicity and perivascular changes in the CNS.

The results of a dedicated study in monkeys evaluating effects on wound healing demonstrated delay in healing of incisions as compared to controls.

4. Clinical Pharmacology

There are no outstanding clinical pharmacology issues that preclude approval. The selected dosing regimen in the proposed product label is adequately supported by nonclinical pharmacodynamic and proof-of-concept studies and results of pharmacokinetic (PK) sampling in the major efficacy trial. The dosing regimen evaluated in the REGARD trial, ramucirumab 8 mg/kg as an intravenous infusion administered every 14 days, was chosen based on the goal of achieving serum trough concentrations of greater than 18 µg/mL; this trough concentration resulted in inhibition of tumor growth in tumor xenograft models. Based on the limited PK sampling collected in a subgroup (n=58) of patients in the ramucirumab arm, 95% of patients achieved the target trough concentration.

The apparent mean half-life of ramucirumab following a single dose of 8 mg/kg was approximately 8 days (range 6-9 days) in Japanese patients with gastric cancer. Population PK did not identify clinically important differences in exposure based on age, gender, or body weight. There was no evidence that ramucirumab exposure resulted in clinically important prolongation of QTc intervals in a dedicated QT study.

Although the incidence of anti-ramucirumab antibody development was evaluated in an adequately sized population, in which the incidence of binding antibodies was 7.4% (33/443) and the incidence of neutralizing antibodies was 3% (1/33 patients with binding antibodies), the reliability of the data is uncertain given the timing of sampling and lack of sensitivity of the assay in the presence of ramucirumab concentrations likely to be present at the time of sampling. Therefore, two post-marketing studies will be required.

5. Clinical/Statistical-Efficacy

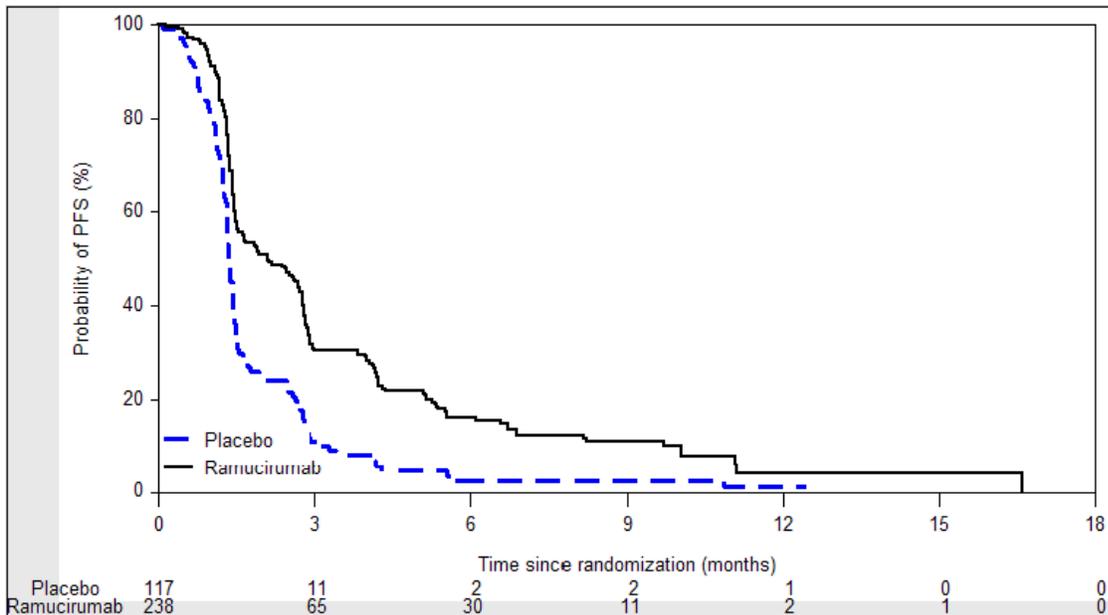
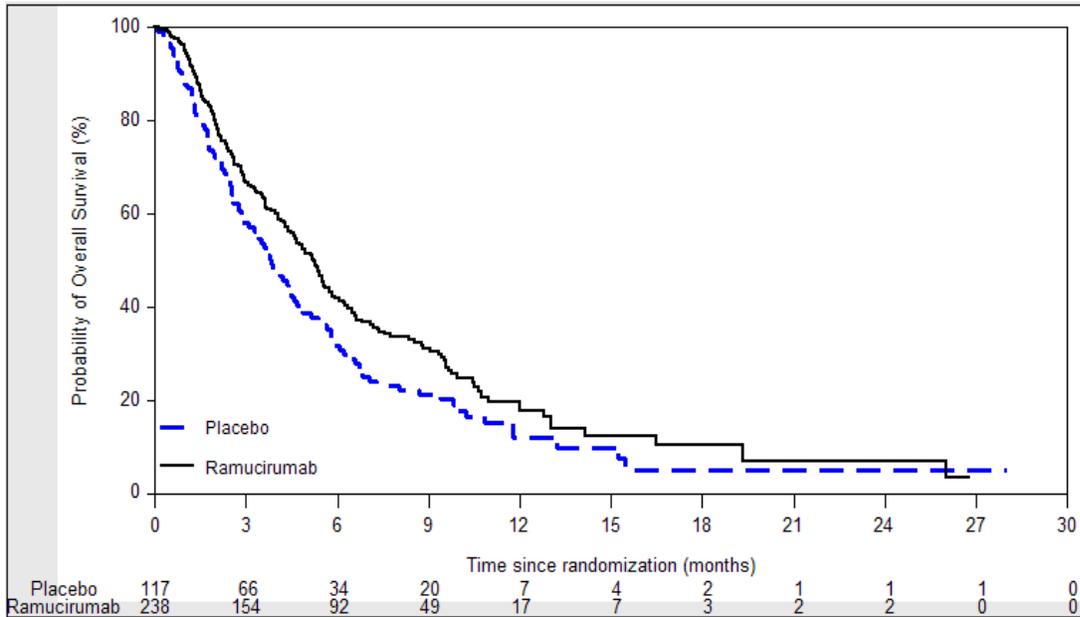
There are no clinical/statistical issues that would preclude approval. The efficacy of ramucirumab was demonstrated in a single multicenter, randomized (2:1), double-blind, placebo-controlled trial (Protocol IMCL CP12-0715/14T-IE-JVBD (REGARD)) evaluating the safety and efficacy of single-agent ramucirumab.

The REGARD trial enrolled 355 patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the gastro-esophageal junction [GEJ]) with disease progression during or within 6 months after completion of platinum- or fluoropyrimidine-containing chemotherapy. Of these 355 patients, 236 were randomized to ramucirumab 8 mg/kg (n=238) as an intravenous infusion every 2 weeks and 117 patients to matching placebo. The trial was conducted at 119 clinical sites across 29 countries. The median age of the study population was 60 years, 70% of patients were male, 77% were White and 16% were Asian; 29% had ECOG performance status of 0 while the remainder had ECOG PS of 1. Across the study population, 91% had measurable disease, the majority, 75%, had gastric cancer and 25% had adenocarcinoma of the GEJ. The majority of patients (85%) had experienced disease progression during or following first-line therapy for metastatic disease. Prior chemotherapy for gastric cancer consisted of platinum/fluoropyrimidine combination chemotherapy (81%), fluoropyrimidine-containing chemotherapy regimens without platinum (15%), or platinum- containing chemotherapy regimens without fluoropyrimidine (4%).

The REGARD trial demonstrated a statistically significant and clinically modest effect on overall survival (OS) [hazard ratio (HR) 0.78 (95% CI 0.60, 0.998), p=0.47] and a more statistically robust but also clinically modest effect on progression-free survival (PFS) [HR = 0.48 (95% CI: 0.38, 0.62), p = < 0.0001]. The observed median survival was 5.2 months for the ramucirumab arm and 3.8 months for the placebo arm, corresponding to a 1.4-month increase in median survival. The observed median PFS was 2.1 months in the ramucirumab arm and 1.3 months in the placebo arm, corresponding to a 0.8- month increase in median PFS. In addition to the modest effect on survival, there was an apparent lack of treatment effects of certain subgroups (women and the patients accrued at North American clinical sites in exploratory subgroup analyses).

The results of the primary and key secondary efficacy analyses are presented in the table and figures below. There was one patient reported to have a complete response and 7 patients reported to have a partial response in the ramucirumab arm for an overall response rate of 3.4%.

| | Ramucirumab N=238 | Placebo N=117 |
|----------------------------------|----------------------|------------------|
| Overall Survival | | |
| Number of deaths (%) | 179 (75%) | 99 (85%) |
| Median – months (95% CI) | 5.2 (4.4, 5.7) | 3.8 (2.8, 4.7) |
| Hazard Ratio (95% CI) | 0.78 (0.60, 0.998) | |
| Stratified Log-rank p-value | 0.047 | |
| Progression-free Survival | | |
| Number of events (%) | 199 (84%) | 108 (92%) |
| Median – months (95% CI) | 2.1 (1.5, 2.7) | 1.3 (1.3, 1.4) |
| Hazard Ratio (95% CI) | 0.48 (0.38, 0.62) | |
| Stratified Log-rank p-value | <0.001 | |



Because of concerns raised by inconsistent treatment effects in specific subsets identified during review of the REGARD trial, and to provide additional support for this single trial, FDA requested and received the high-level summary results (and limited datasets) of a second, multicenter, randomized, double-blind, placebo-controlled trial (RAINBOW) evaluating the contribution of ramucirumab to chemotherapy over chemotherapy alone. Both trials were conducted in patients with metastatic gastric/GEJ adenocarcinoma which had progressed following one prior chemotherapy regimen for treatment of metastatic disease and demonstrated a statistically significant, modest increase in OS.

Protocol CP12-0922/I4T-IE-JVBE (RAINBOW) is a randomized (1:1) multicenter, multinational, double-blind, placebo-controlled trial that evaluated the safety and efficacy of ramucirumab 8 mg/kg every two weeks in combination with paclitaxel compared with paclitaxel alone in 665 patients with previously treated metastatic or unresectable, locally advanced gastric cancer. The final analysis of this trial demonstrated a statistically significant effect on survival [HR 0.81 (0.68, 0.96), $p = 0.02$] and PFS [HR 0.64 (0.54, 0.75), $p < 0.0001$]; the effects on OS were consistently observed across relevant subgroups, including women and patients enrolled at clinical sites in North America, Europe, or Australia.

6. Safety

The safety of ramucirumab as a single agent was evaluated in 570 patients, including 236 patients with locally advanced or metastatic gastric or GEJ adenocarcinoma, with an ECOG performance status of less than or equal to 1, who received ramucirumab in Study I4T-IE-JVBD. The most common adverse reactions (all grades) observed in ramucirumab-treated patients at a rate of greater than or equal to 10% and greater than or equal to 2% higher than placebo were hypertension and diarrhea. The grade 3-4 adverse reactions reported at a higher incidence in the ramucirumab arm (greater than or equal to 2% difference between arms) included hypertension and hyponatremia. The most common serious adverse events with ramucirumab were intestinal obstruction (2.1%) and anemia (3.8%). Other important risks described in labeling include hemorrhage (see below), arterial thrombotic events, infusion-related reactions, gastrointestinal perforation, impaired wound healing, clinical deterioration in patients with cirrhosis, and reversible posterior leukoencephalopathy.

The incidence of severe (NCI CTCAE grade 3) hemorrhage was higher for ramucirumab-treated patients (3.4% vs. 2.6%) as was the incidence of patients receiving red blood cell transfusions (11% vs. 8.7%). Based on these findings, FDA requested that labeling contain a Boxed Warning for Hemorrhage.

7. Advisory Committee Meeting

This new molecular entity was not referred to the Oncologic Drugs Advisory Committee because the application did not raise significant public health questions on the role of ramucirumab for the treatment of patients with relapsed or refractory metastatic gastric adenocarcinoma, and outside expertise was not necessary since there were no controversial issues that would benefit from advisory committee discussion.

8. Pediatrics

On February 16, 2012, Imclone Systems LLC received orphan drug designation for treatment of gastric cancer; therefore, this application is exempt from the requirements of the Pediatric Research Equity Act (PREA).

9. Labeling

- Proprietary name: The proposed proprietary name, Cyramza, was determined to be acceptable by DMEPA, OPDP, and the clinical review team members.
- Physician labeling – all major labeling issues were resolved and labeling comments from all disciplines, including OPDP and OSE were addressed during labeling meetings.

10. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.
- Risk Benefit Assessment
This approval is based on the demonstration of improved OS in a multinational, randomized (2:1), double-blind, multicenter study (I4T-IE-JVBD) enrolling 355 patients with previously treated advanced or metastatic, gastric or GEJ adenocarcinoma. The median OS was 5.2 months in the ramucirumab plus best supportive care (BSC) arm and 3.8 months in the placebo plus BSC arm [HR 0.78 (95% CI: 0.60, 0.998), $p=0.047$, stratified log rank test]. Median PFS was longer in the ramucirumab arm compared to the placebo arm [HR 0.48 (95% CI: 0.38, 0.62), $p < 0.001$, stratified log rank test]. The magnitude of the treatment effect on survival and PFS are modest, however, they may be meaningful to patients whose median survival is only 3.8 months and median PFS is only 1.3 months. In addition, based on the common side effects (hypertension, diarrhea, and headache with an incidence of $\leq 16\%$ each) and of the low incidence of serious adverse drug reactions of anemia (3.8%), severe bleeding (3.4%), and intestinal obstruction (2.1%), the toxicity profile is acceptable to patients and physicians, given the benefits and limited survival in the indicated population of less than one year.

The risk-benefit was also deemed favorable by Drs. Keegan, Lemery and Casak. Additionally, all review team members recommend approval of this application, and I concur with their recommendation.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
None.
- Recommendation for other Postmarketing Requirements and Commitments
See action letter.

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/s/

TAMY E KIM
04/21/2014

RICHARD PAZDUR
04/21/2014