

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125477Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: February 27, 2014

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Subject: Evaluation to determine if a REMS is necessary

Drug Name(s): Cyramza (ramucirumab /IMC-1211)

Therapeutic Class: Monoclonal antibody targeting VEGFR-2

Dosage and Route: 8 mg/kg IV every 2 weeks

Application Type/Number: BLA 125477

Applicant/sponsor: Eli Lilly

OSE RCM #: 2013-1961

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity Cyramza (ramucirumab). The Agency received an original Biologics License Application (BLA) from Eli Lilly (Lilly) for ramucirumab on August 23, 2013 as a rolling submission. The proposed indication is for the treatment of patients with advanced gastric or gastro-esophageal junction adenocarcinoma, as a single-agent after prior chemotherapy. To date ramucirumab has not been approved in any country.

Eli Lilly submitted an EU Risk Management Plan, but did not submit a proposed REMS with this application. (b) (4)

1.1 BACKGROUND

In 2014, it is estimated in the United States there will be 22,000 new cases of gastric cancer and approximately 11,000 will die of this disease. The five year survival rate for gastric cancer is 28% for patients with disease that has invaded regional tissue and only 4% for advanced disease or metastatic disease.¹

The following is a summary of drugs that contain labeling relevant to the treatment of gastric cancer in the indication section of their label.

- docetaxel- *indicated with cisplatin* and fluorouracil for untreated advanced gastric cancer, including gastroesophageal junction*
- doxorubicin hydrochloride – *indicated alone or in combination with other chemotherapy for metastatic gastric cancer*
- fluorouracil – *effective in the palliative management of the carcinoma of the colon, rectum breast, stomach and pancreas*
- trastuzumab - *indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease.*
- mitomycin - *for injection is not recommended as single-agent, primary therapy. It has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.*

* Cisplatin labeling does not include gastric cancer

If approved, ramucirumab would be the only approved treatment for patients with advanced or metastatic disease that has progressed after first line therapy.

National Comprehensive Cancer Network practice guidelines for the treatment of metastatic gastric cancer generally recommend a two drug regimen with fluoropyrimidine and a platinum

¹ Cancer Facts and Figures 2014 accessed on Feb 15, 2014 at <http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-041770.pdf>

chemotherapy.² Depending on the patient's performance status a third drug, docetaxel or irinotecan could be added. In addition, trastuzumab is considered when a patient has HER2-neu overexpressing adenocarcinoma. NCCN second-line treatment options include options for single agent and combination therapy however, the NCCN panel concluded there is no evidence to support any specific regimen for second line therapy. Advanced and metastatic gastric cancer is a fatal disease. In addition to best supportive care, the treatment for patients with advanced gastric cancer is a balance between efforts to prolong survival and toxicity.

The vascular endothelial growth factor (VEGF) pathway regulates vasculogenesis and angiogenesis. VEGF's function is to create new vessels during fetal development, after injury or develop collateral circulation to bypass blocked vessels. Stimulation of the VEGF pathway is overexpressed in many human tumors which enables tumor growth and the ability to metastasize.

Ramucirumab is a recombinant human monoclonal antibody of the Ig1 class which is a receptor-targeted antibody that blocks vascular endothelial growth factor Receptor 2 (VEGFR-2). If approved, ramucirumab would be the only approved treatment for patients with advanced or metastatic disease that has progressed after first line therapy. The recommended dosing regimen is 8 mg/kg every two weeks (q2w) administered as an intravenous (IV) infusion over 60 minutes.

1.2 REGULATORY HISTORY

On August 23, 2013, the Agency received the last module of a rolling submission for an original Biologics License Application (BLA) for the use of ramucirumab for the treatment of patients with advanced gastric cancer and gastro-esophageal junction adenocarcinoma as a single-agent after prior chemotherapy.

The applicant was granted orphan drug designation for the treatment of patients with gastric cancer on February 16, 2012 and on November 14, 2012 the FDA granted Fast Track designation to the application for the treatment of gastric cancer. The review classification for the application is Priority.

2 MATERIALS REVIEWED

- August 23, 2013, Original BLA 125477 submission. Sections reviewed include:
 - Section 1.14, Draft labeling
 - Section 1.16 EU Risk Management Plan
 - Section 2.5, Clinical Overview
 - Section 2.7.4, Summary of Clinical Safety
- Clinical Review by Sandra Casak, signed in DARRTs January 16, 2014
- Statistical Review by Hui Zhang and Kun He, signed in DARRTs January 23, 2014
- Clinical Pharmacology Review by Lillian Zhang, Ph.D., signed in DARRTs January 23, 2014
- Interdisciplinary Review Team for QT Studies Consultation: QT Study Review by Marathe, Krudys, Dang, Fiszman and Stockbridge signed in DARRTs August 19, 2013.

² National Comprehensive Cancer Network (version 2.2013, accessed on Feb 15, 2014 at http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf)

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

Please refer to Dr. Casak's review for the full clinical review of efficacy and safety.

The pivotal trial REGARD, demonstrated the efficacy of ramucirumab in a Phase 3, randomized, double-blind trial of ramucirumab plus best supportive care (BSC) versus placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction adenocarcinoma following disease progression on first-line platinum- or fluoropyrimidine-containing combination therapy. In the trial, the primary efficacy endpoint was overall survival (OS), and the secondary objectives were progression free survival, response rate and a comparison of the safety profile. The study arms were balanced with regard to patient demographic and all patients had a diagnosis of adenocarcinoma. Patients received treatment until disease progression, intolerable toxicity, or patient refusal of therapy. Patients who received ramucirumab plus BSC (N=238) had a statistically significant improvement in OS as compared to patients receiving placebo plus BSC (N = 117) with a hazard ratio of 0.78; (95% CI: 0.60 to 1.00) and a p-value of 0.047. The median overall survival in the ramucirumab arm was 5.2 months versus 3.8 months in the placebo arm. Median time to disease progression in the ramucirumab arm was 2.1 months (95% CI 1.5; 2.7) versus 1.3 months in the placebo arm (95% CI 1.3, 1.4).

High-level results from a separate trial, RAINBOW, (randomized multicenter, double-blinded, placebo-controlled, Phase 3 study of weekly paclitaxel with or without ramucirumab in patients with metastatic gastric adenocarcinoma refractory or progressive after first-line therapy with platinum and fluoropyrimidine) support the improvement in overall survival for patients treated with ramucirumab.

3.2 SAFETY

The sponsor stated in their EU Risk Management Plan that a total of 3777 patients have received ramucirumab over the entire clinical trial development program. Dr. Casak's safety analysis was comprised of findings from the pivotal trial REGARD, and data from an additional 334 patients who received ramucirumab as a single agent in Phase 1 and 2 studies.

3.2.1 Safety Analysis of REGARD

Due to disease progression only a small population of patients (n=33) received treatment for greater than 6 months. Sixty-four percent of the patients in the placebo arm and 63% of the patients in the ramucirumab arm died due to disease progression. In REGARD the most frequent reason to discontinue therapy was disease progression (ramucirumab 53% and placebo 62%). The safety analysis database indicated that 14% of patients receiving ramucirumab and 6% of patients on placebo stopped treatment due to an adverse event. The incidence of non-fatal adverse events were the same in both arms (38%), fatal outcomes were slightly greater for ramucirumab (11% vs 10%) when disease-related events are removed. The most common adverse events ($\geq 10\%$) at all grades observed in patients who received ramucirumab compared to placebo are fatigue, decreased appetite, vomiting, abdominal pain, diarrhea and constipation. Rates of vomiting, abdominal pain, diarrhea and constipation were greater in the placebo arm than in the ramucirumab arm. The incidence of fatigue and decreased appetite was similar in both arms. Dr.

Casak’s subgroup analysis of adverse events did not show any appreciable difference when age, gender, geographic region and tumor location were considered. There were no cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) reported in REGARD. Table 1 contains a summary of adverse events of concern.

Table 1
Adverse Events of Concern

Study	REGARD	
	Ramucirumab arm	Placebo arm
Event		
Arterial thromboembolic events	4 patients (6 events)	0 patients
Venous thromboembolic events	9 patients	8 patients
Bleeding/Hemorrhagic events	16%	11%
Grade 1-2	12%	8%
Fatal gastrointestinal hemorrhage	1 patient	1 patient
Hypertension	17%	8%
Grade 3 only	8%	3%
Grade 4	0	0
Gastrointestinal Perforation	2 patient (fatal)	1 patient (fatal)
Proteinuria	3%	2.6%
Hepatic events (Grade 3-4)	8%	7%

3.2.2 Pooled Safety Analysis from Single Agent Therapy Phase 1 and 2 Studies

The safety evaluation of the patients from the Phase 1 and 2 studies (N=191) are more difficult to interpret because patients varied with regard to disease (e.g., ovarian, renal cell), dosing regimen (e.g, QT study vs. dose-escalation studies) and prior treatment. The incidence of bleeding/hemorrhagic events was 48% in the pooled analysis, with 4% experiencing a Grade 3 or greater event. Hypertension was reported in 29%, with 10% of this patient population experiencing Grade 3-4 hypertension. Liver disorder as per the Standardized MedDRA Query (SMQ) was reported for 27 out of 191 patients. Eleven of the patients who experienced Grade ≥ 3 events, had hepatocellular carcinoma. Fourteen percent of the patients were reported to have proteinuria, with 2% experiencing Grade 3-4 proteinuria. Dr. Casak summarized, the events from Phase 1 and 2 studies are similar to the safety findings from REGARD.

3.2.3 Electrocardiograms

A multicenter, open-label study evaluated the relationship between ramucirumab (monotherapy 10mg/kg Q 3 weeks for 9 weeks) and corrected QT interval changes in patients with advanced cancer (n=68). No significant QTc prolongation effect of ramucirumab (10 mg/kg/3 weeks) was detected in this QT study. Please refer to the interdisciplinary review by Marathe, Krudys, Dang, Fiszman and Stockbridge.

3.2.4 Liver Injury/failure

The multicenter, randomized, double-blind, Phase 3 study of ramucirumab vs. BSC as a second-line treatment in patients with hepatocellular carcinoma following first-line treatment with sorafenib had an imbalance in hepatic events (9.6% ramucirumab, 2.9% placebo). Lilly was

asked to submit an aggregated safety report for liver toxicity for patients treated for cancers that were not hepatocellular carcinoma. An unblinded review of 13 cases revealed that 11 cases occurred in patients who received ramucirumab and 2 cases in placebo arms. All cases of non-hepatocellular carcinoma liver toxicity were confounded by concurrent use of hepatotoxic drugs and metastatic disease. The conclusion was that ramucirumab may not directly cause drug-induced liver injury but can exacerbate sequelae of cirrhosis.

3.2.5 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

There were two RPLS events from the global safety data base. One was a Grade 2 which occurred with hypertension and improved after treatment, the other case was later relabeled to cerebral infarction.

3.2.6 Gastrointestinal Hemorrhage

Lilly provided preliminary findings of RAINBOW including an imbalance in gastrointestinal hemorrhage in the ramucirumab arm. Lilly has proposed to include gastrointestinal bleeding in the severe bleeding section of Warnings and Precautions of the label.

3.2.7 Fetal development

No animal studies were conducted to assess the impact of ramucirumab on fetal development. Although it is unknown if ramucirumab will have an effect on fetal development, based on the drug's mechanism, it is likely to result in untoward effects on the fetus if used during pregnancy.

4 DISCUSSION

4.1 Benefit

Ramucirumab is a human receptor-targeted antibody that blocks VEGFR 2 indicated for the treatment of advanced gastric cancer or gastro-esophageal junction adenocarcinoma, as a single-agent therapy after prior fluoropyrimidine- and cisplatin-containing chemotherapies. Advanced or metastatic gastric cancer is almost always fatal. There is no standard treatment for patients with advanced or metastatic disease that progresses beyond treatment with fluoropyrimidine- and cisplatin-containing chemotherapies. Patients who received ramucirumab plus BSC had a statistically significant improvement in overall survival as compared to patients receiving placebo plus BSC; the median overall survival in the ramucirumab arm was 5.2 months versus 3.8 months in the placebo arm. These findings are supported by high-level findings from the RAINBOW study. In summary, ramucirumab appears to offer a treatment option for patients with advanced/metastatic gastric cancer that progress after previous therapy.

4.2 Risks

Adverse events of special concern include arterial and thromboembolic events, hemorrhage and bleeding, hypertension, gastrointestinal perforation, hepatic injury/failure impairment, RPLS, proteinuria and embryo-fetal toxicity. Although the number of patients are limited, the adverse events reported are consistent with toxicity and safety profile of approved agents, both small molecule and monoclonal antibodies, that target the VEGF pathway.

The Warning and Precautions sections of the labels for approved agents that interfere with the VEGF pathway are similar (Appendix A). At the time of this review the Warnings and Precautions section of the proposed label for ramucirumab includes arterial thromboembolic events, hypertension, infusion related reactions, gastrointestinal perforation, hemorrhage, impaired wound healing, clinical decompensation in patients with Child-Pugh B or C cirrhosis and RPLS.

Vandetanib, which targets VEGF, was approved with a REMS for the risk of prolonged QT interval, Torsades de pointes, and sudden death. The elements of the vandetanib REMS includes a Medication Guide, communication plan and elements to assure safe use. Vandetanib is indicated for the treatment of symptomatic or progressive medullary thyroid cancer (MTC) in patients with unrespectable locally or advanced metastatic disease and the use vandetanib in patients within indolent, asymptomatic or slowly progressing disease only after careful consideration of the treatment of related risk of vandetanib. The 5 year survival rate for Stage IV MTC disease is 28%.³ The risk benefit profile is different for vandetanib patients with MTC, which is measured in years versus months for advanced gastric cancer. No significant QTc prolongation effect was detected the QT study for ramucirumab.

Based on the available safety information DRISK does not recommend a REMS for management of the risks associated with ramucirumab. The safety profile is consistent with similar agents that target VEGF, and all but one is approved without a REMS. It appears to have an acceptable safety profile for patients with advanced gastric or gastro-esophageal junction adenocarcinoma, as a single-agent after prior chemotherapy. Third, the likely prescribers are oncologists who, because of the number of approved VEGF agents, are familiar and knowledgeable about managing the risks associated with drugs that interfere with the VEGF pathway.

5 CONCLUSION

DRISK concurs with the Division of Oncology Products-2 that, based on the available data and the potential benefits and risks of treatment, at this time a REMS is not necessary for ramucirumab. If new safety information becomes available this recommendation can be re-evaluated.

³American Cancer Society <http://www.cancer.org/cancer/thyroidcancer/detailedguide/thyroid-cancer-survival-rates> Accessed February 27, 2014.

Appendix A

Approved Drugs that Target Vascular Endothelial Growth Factor (VEGF)

Drug (tradename/ approval date)	Indication (Indications and use section of the label)	Class	Target	Warnings/ Precautions (included in Boxed Warning)	REMS
Afilbercept (Eylea/2011, Zaltrap/2010)	Neovascular wet AMD; Macular Edema following central retinal vein occlusion - intravitreal injection (1) (Eylea) Metastatic colorectal cancer(1) (Zaltrap)	Recombinant fusion protein of VEGF 1 and 2 fused to IgG 1 large molecule (115kDa)	VEGF A, B, PIGF inhibition	<u>Hemorrhage,</u> <u>Perforation,</u> <u>Compromised wound healing,</u> Fistula Formation, Hypertension, Arterial Thromboembolic Events, Proteinuria, Neutropenia and Neutropenic Complications, Diarrhea and Dehydration, RPLS*, Pregnancy Category C	No
Axitinib (Inlyta/2012)	Advanced renal cell carcinoma after failure of one prior systemic therapy (1)	Small molecule	VEGFR1, VEGFR2, VEGFR3,PDGF RB, c-KIT	Hypertension and hypertensive crisis, Arterial thrombotic events, Venous thrombotic events Hemorrhage, Gastrointestinal perforation and fistula formation Thyroid dysfunction, Wound healing complications, RPLS*, Proteinuria , Elevation of liver enzymes, Hepatic Impairment, Pregnancy –fetal harm	
Bevacizumab (Avastin/2004)	Metastatic colorectal cancer, with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment. (1.1) Non-squamous non-small cell lung cancer, with carboplatin and	Monoclonal Antibody	VEGF	<u>GI Perforation,</u> <u>Surgery and wound healing complications,</u> <u>Hemorrhage,</u> Non-GI Fistula formation, Arterial Thromboembolic Events, Hypertension, RPLS,	No

	<p>paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease. (1.2)</p> <p>Glioblastoma, as a single agent for adult patients with progressive disease following prior therapy. (1.3)</p> <p>Metastatic renal cell carcinoma with interferon alfa (1.4)</p>			<p>Proteinuria, Infusion Reactions, Ovarian Failure</p>	
<p>Cabozantinib (Cometriq/2012)</p>	<p>Progressive, metastatic medullary thyroid cancer (1)</p>	<p>Small molecule</p>	<p>RET, MET, VEGFR, KIT, TRKB, FLT, AXL, and TIE.</p>	<p><u>Perforations and fistulas, Hemorrhage,</u> Thrombotic events, Wound complications, Hypertension, Osteonecrosis of the jaw, Palmar-Plantar Erythrodysesthesia, Proteinuria, RPLS*, Drug interactions, Hepatic impairment, Embryo- fetal toxicity</p>	<p>No</p>
<p>Pazopanib (Votrient/2009)</p>	<p>Advanced renal cell carcinoma (1)</p> <p>Advanced soft tissue sarcoma who have received prior chemotherapy (1)</p>	<p>Small molecule</p>	<p>VEGFR2/PDGF R/c-kit</p>	<p><u>Hepatotoxicity and Hepatic Impairment,</u> Prolonged QT intervals and torsades de Pointes, Cardiac dysfunction, Hemorrhagic events, Arterial thrombotic events, Venous thromboembolic events, Thrombotic microangiopathy, Gastrointestinal perforation or fistula, RPLS*, Hypertension, Wound healing,</p>	<p>No</p>

				Hypothyroidism, Proteinuria, Infection: Serious infections (with or without neutropenia, Increased toxicity with other cancer therapy, Increased toxicity in developing organs, Pregnancy- embryo-fetal toxicity	
Ranibizumab (Lucentis/2006)	Neovascular (Wet) Age-Related Macular Degeneration (1.1) Macular Edema Following Retinal Vein Occlusion (1.2) Diabetic Macular Edema (DME) (1.3)	Monoclonal antibody	VEGF	Endophthalmitis and retinal detachments , Increases in intraocular pressure, Thromboembolic events, Fatal events in DME patients	NO
Regorafenib (Stivarga/2012)	Metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliptain, and irinotecan-based chemotherapy, an anti-VEGF therapy, and if KRAS wild type, an anti-EGFR therapy (1.1) Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imiatinib and sunitinib. (1.2)	Small molecule	VEGFR-1,2,3, TIE2 KIT, RET, RAF-1, BRAF, BRAFV600E	Hepatotoxicity, Hemorrhage Dermatological toxicity, Hypertension, Cardiac ischemia and infarction, RPLS*, GI perforation or fistulae, Wound healing complications, Embryo-fetal toxicity	No
Sorafenib (Nexavar/2005)	Unresectable hepatocellular carcinoma (1.1) Advanced renal cell carcinoma (1.2) Locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive	Small molecule	multiple targets	Cardiac ischemia and/or infarction, Hemorrhage, Hypertension, Dermatologic Toxicities, Gastrointestinal perforation, Warfarin, Wound healing complications, Increased mortality observed when	

	iodine treatment (1.3)			administered in combination with carboplatin/paclitaxel and gemcitabine/cisplatin in squamous cell lung cancer, QT Prolongation, Drug-induced hepatitis, Embryofetal risk	
Sunitinib (Sutent/2006)	Gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate. (1.1) Advanced renal cell carcinoma (RCC). (1.2) Progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease. (1.3)	Small molecule	multiple targets	Hepatotoxicity, Embryofetal toxicity, Left Ventricular Dysfunction, Prolonged QT intervals and Torsade de Pointes, Hypertension, Hemorrhagic events, Osteonecrosis of the jaw, Tumor Lysis Syndrome, Thyroid dysfunction, Wound healing, Adrenal toxicity, Laboratory tests	REMS eliminated May 2011**
Vandetanib (Caprelsa/2011)	Symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.	Small molecule	RET, VEGFR, EGFR	<u>Prolonged QT Interval, Torsades de pointes, and sudden death,</u> Skin Reactions and Stevens-Johnson syndrome, Interstitial lung disease, Ischemic cerebrovascular events, Hemorrhage, Heart failure Diarrhea, Hypothyroidism, Hypertension, RPLS*, Drug Interactions, Renal impairment,	REMS with MG, CP and ETASU ** *

				Hepatic Impairment, Embryofetal toxicity CAPRELSA REMS for risk of prolonged QT Interval, Torsades de pointes, and sudden death	
* Reversible Posterior Leukoencephalopathy Syndrome (RPLS) ** Medication Guide only REMS ***MG, Communication Plan and Elements to assure safe use (ETASU)					

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/s/

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