



November 5, 2014

Lilly's CYRAMZA® (ramucirumab) in Combination with Paclitaxel Granted FDA Approval for Advanced Gastric Cancer After Prior Chemotherapy

CYRAMZA now approved both as a single-agent treatment and in combination with chemotherapy

INDIANAPOLIS, Nov. 5, 2014 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today that the U.S. Food and Drug Administration (FDA) has approved CYRAMZA® (ramucirumab) in combination with paclitaxel (a type of chemotherapy) as a treatment for people with advanced or metastatic gastric (stomach) or gastroesophageal junction (GEJ) adenocarcinoma whose cancer has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy. CYRAMZA now has two FDA approvals for these patients. Today's announcement follows the April approval of CYRAMZA as a single agent - the first approval of a treatment in the U.S. for patients in this setting.

"This FDA approval of CYRAMZA represents another milestone for people battling this devastating and difficult-to-treat disease," said Richard Gaynor, M.D., senior vice president, product development and medical affairs for Lilly Oncology. "Lilly is pleased to continue delivering on its commitment to provide new treatment options to people living with cancer and those who care for them."

Stomach cancer is the fifth most common cancer in the world and is the third-leading cause of cancer death.ⁱ In the U.S., approximately 22,000 people will be diagnosed with stomach cancer in 2014.ⁱⁱ CYRAMZA (ramucirumab injection 10 mg/mL solution) is the only FDA-approved second-line treatment option for patients with advanced or metastatic gastric or GEJ adenocarcinoma whose disease has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

This FDA approval for CYRAMZA is based on the Phase III RAINBOW trial, which compared CYRAMZA plus paclitaxel to placebo plus paclitaxel. Efficacy endpoints in the trial included the major efficacy outcome measure of overall survival and the supportive efficacy outcome measures of progression-free survival and objective response rate. The labeling for CYRAMZA contains a Boxed Warning regarding increased risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. CYRAMZA should be permanently discontinued in patients who experience severe bleeding. See the Important Safety Information at the end of this press release and the [Prescribing Information](#).

CYRAMZA has been granted Orphan Drug Designation by the FDA for this indication. Orphan drug status is given in the U.S. by the FDA's Office of Orphan Products Development (OOPD) to medicines that show promise for the treatment of rare diseases.

Lilly is committed to offering patient assistance programs for eligible patients receiving CYRAMZA treatment. Patients, physicians, pharmacists or other healthcare professionals with additional questions about CYRAMZA should contact The Lilly Answers Center at 1-800-LillyRx (1-800-545-5979) or visit www.lilly.com. Healthcare professionals may also find additional product information on CYRAMZA at www.CYRAMZA.com.

About CYRAMZA® (ramucirumab)

CYRAMZA as a single agent, or in combination with paclitaxel (a type of chemotherapy), is approved for the treatment of people with advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose cancer has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

CYRAMZA is an antiangiogenic therapy. It is a vascular endothelial growth factor (VEGF) Receptor 2 antagonist that specifically binds and blocks activation of VEGF Receptor 2, by blocking the binding of VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D. CYRAMZA inhibited angiogenesis in an *in vivo* animal model.

About Angiogenesis

Angiogenesis is the process of making new blood vessels. In a person with cancer, angiogenesis creates new blood vessels that give a tumor its own blood supply, allowing it to grow and spread.

Some tumors create proteins called VEGF. These proteins attach to the VEGF receptors of blood vessel cells causing new blood vessels to form around the tumors, enabling growth. Blocking the VEGF protein from linking to the blood vessels helps to inhibit tumor growth by slowing angiogenesis and the blood supply that feeds tumors. Of the three known VEGF receptors,

VEGF Receptor 2 is linked most closely to VEGF-induced tumor angiogenesis.

About RAINBOW

RAINBOW was a multinational, randomized, double-blinded, placebo-controlled Phase III study of CYRAMZA plus paclitaxel compared to placebo plus paclitaxel in people with locally advanced or metastatic gastric or GEJ adenocarcinoma, whose cancer had progressed after fluoropyrimidine- and platinum-containing chemotherapy. Initiated in 2010, the global study randomized a total of 665 patients across 27 countries in North America, South America, Europe, Australia and Asia. RAINBOW is the first Phase III study to demonstrate a survival benefit with a biologic used in combination with chemotherapy in this setting.

CYRAMZA plus paclitaxel significantly extended median overall survival compared with placebo plus paclitaxel (9.6 months [95% confidence interval (CI): 8.5, 10.8] vs. 7.4 months [95% CI: 6.3, 8.4], respectively; hazard ratio 0.81 [95% CI: 0.68, 0.96]; $P=0.017$). Furthermore, CYRAMZA plus paclitaxel significantly delayed disease progression (progression-free survival of 4.4 months for CYRAMZA plus paclitaxel [95% CI: 4.2, 5.3] vs. 2.9 months for placebo plus paclitaxel [95% CI: 2.8, 3.0]; hazard ratio 0.64 [95% CI: 0.54, 0.75]; $P < 0.001$). Significantly more patients responded to CYRAMZA combined with paclitaxel than with paclitaxel alone (28% [95% CI: 23, 33] for CYRAMZA plus paclitaxel vs. 16% [95% CI: 13, 20] for placebo plus paclitaxel; $P < 0.001$). The percentage of deaths at the time of analysis was 78% (256 patients) and 78% (260 patients) in the CYRAMZA-plus-paclitaxel and placebo-plus-paclitaxel treatment arms, respectively. The progression-free survival number of events was 279 (85%) and 296 (88%) for the CYRAMZA-plus-paclitaxel and placebo-plus-paclitaxel treatment arms, respectively.

The labeling for CYRAMZA contains a Boxed Warning for hemorrhage and additional Warnings and Precautions for arterial thromboembolic events, hypertension, infusion-related reactions, gastrointestinal perforations, impaired wound healing, clinical deterioration in patients with Child-Pugh B or C cirrhosis, and reversible posterior leukoencephalopathy syndrome. In the RAINBOW trial, the most common adverse reactions (all grades) observed in patients treated with CYRAMZA plus paclitaxel at a rate of $\geq 30\%$ and $\geq 2\%$ higher than placebo plus paclitaxel were fatigue (57% vs. 44%), neutropenia (low white blood cell count) (54% vs. 31%), diarrhea (32% vs. 23%), and epistaxis (bleeding from the nose) (31% vs. 7%). The most common serious adverse events with CYRAMZA plus paclitaxel in the RAINBOW trial were neutropenia (3.7%) and febrile neutropenia (fever and potentially other infection signs along with low white blood cell count) (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors (treatment for low white blood cells). See the Important Safety Information at the end of this press release and the [Prescribing Information](#).

About Gastric Cancer

Gastric (stomach) cancer is a major health problem. It is the fifth most common cancer in the world and is the third-leading cause of cancer death. There were nearly one million new cases worldwide in 2012 (631,000 men, 320,000 women) with approximately 723,000 deaths (469,000 men, 254,000 women).ⁱⁱⁱ Stomach cancer is more prevalent in countries outside the U.S. and EU.^{iv} In the U.S., it is estimated that approximately 22,000 people will be diagnosed with gastric cancer in 2014.^v

Gastric cancer is a disease in which cancer cells form in the stomach. It develops slowly, usually over many years, and often goes undetected.^{vi} As stomach cancer advances, it can travel through the bloodstream and spread to organs such as the liver, lungs and bones.^{vii} The most common type of stomach cancer is called adenocarcinoma, which starts from one of the common cell types found in the lining of the stomach.^{viii}

Lilly PatientOne

The Lilly PatientOne program addresses financial and coverage issues for qualified uninsured, underinsured and insured patients who are prescribed a Lilly Oncology product. Lilly PatientOne provides reimbursement assistance for eligible patients who are prescribed a Lilly Oncology product, such as information about coding and billing, prior authorization, benefits investigation, and denied claim appeals, as well as operating a patient assistance program. To learn more, visit www.LillyPatientOne.com or call 1-866-4PatOne (1-866-472-8663).

Indication

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE

CYRAMZA increased the risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In Study 1, which evaluated CYRAMZA as a single agent in advanced gastric cancer, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In Study 2, which evaluated CYRAMZA plus paclitaxel, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroid anti-inflammatory drugs (NSAIDs) were excluded from enrollment in Studies 1 and 2; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events

- Serious, sometimes fatal, arterial thromboembolic events (ATEs) including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in Study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) as compared to placebo (3%) and in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, infusion-related reactions (IRRs) occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for Grade 3 or 4 IRRs.

Gastrointestinal Perforations

- CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Four of 570 patients (0.7%) who received CYRAMZA as a single agent in clinical trials experienced gastrointestinal perforation. In Study 2, the incidence of gastrointestinal perforations was also increased in patients who received CYRAMZA plus paclitaxel (1.2%) as compared to patients who received placebo plus paclitaxel (0.3%). Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA is an antiangiogenic therapy with the potential to adversely affect wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Child-Pugh B or C Cirrhosis

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- RPLS has been reported at a rate of < 0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Most Common Adverse Reactions—Single Agent

- The most commonly reported adverse reactions (all grades; grade 3-4) occurring in ≥5% of patients receiving CYRAMZA and ≥2% higher than placebo in Study 1 were hypertension (16% vs 8%; 8% vs 3%), diarrhea (14% vs 9%; 1% vs 2%), headache (9% vs 3%; 0% vs 0%), and hyponatremia (6% vs 2%; 3% vs 1%).
- The most common serious adverse events with CYRAMZA in Study 1 were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in ≥1% and < 5% of CYRAMZA-treated patients in Study 1 were: neutropenia (4.7% vs 0.9%), epistaxis (4.7% vs 0.9%), rash (4.2% vs 1.7%), intestinal obstruction (2.1% vs 0%), and arterial thromboembolic events (1.7% vs 0%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions. In Study 1, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in Study 1 was 0.8% and the rate of infusion-related reactions was 0.4%.

Most Common Adverse Reactions—Combination with Paclitaxel

- The most commonly reported adverse reactions (all grades; grade 3-4) occurring in ≥5% of patients receiving CYRAMZA plus paclitaxel and ≥2% higher than placebo plus paclitaxel in Study 2 were fatigue/asthenia (57% vs 44%; 12% vs 6%), neutropenia (54% vs 31%; 41% vs 19%), diarrhea (32% vs 23%; 4% vs 2%), epistaxis (31% vs 7%; 0% vs 0%), hypertension (25% vs 6%; 15% vs 3%), peripheral edema (25% vs 14%; 2% vs 1%), stomatitis (20% vs 7%; 1% vs 1%), proteinuria (17% vs 6%; 1% vs 0%), thrombocytopenia (13% vs 6%; 2% vs 2%), hypoalbuminemia (11% vs 5%; 1% vs 1%), and gastrointestinal hemorrhage events (10% vs 6%; 4% vs 2%).
- The most common serious adverse events with CYRAMZA plus paclitaxel in Study 2 were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA plus paclitaxel combination in 2% or more patients in Study 2 were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and < 5% of the CYRAMZA plus paclitaxel-treated patients in Study 2 were sepsis (3.1% for CYRAMZA plus paclitaxel vs 1.8% for placebo plus paclitaxel) and gastrointestinal perforations (1.2% for CYRAMZA plus paclitaxel vs 0.3% for placebo plus paclitaxel).

Drug Interactions

- No pharmacokinetic (PK) interactions were observed between ramucirumab (CYRAMZA) and paclitaxel.

Use in Specific Populations

- Pregnancy Category C: Based on its mechanism of action, CYRAMZA may cause fetal harm. Advise females of reproductive potential to avoid getting pregnant, including use of adequate contraception, while receiving CYRAMZA and for at least 3 months after the last dose of CYRAMZA. Animal models link angiogenesis, VEGF and VEGF Receptor 2 to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no adequate or well-controlled studies of ramucirumab in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.
- Nursing Mothers: It is recommended to discontinue nursing or discontinue CYRAMZA due to the potential risks to the nursing infant.
- Females of Reproductive Potential: Advise females of reproductive potential that CYRAMZA may impair fertility.

Please see full Prescribing Information for CYRAMZA, including Boxed Warning for hemorrhage, at <http://pi.lilly.com/us/cyramza-pi.pdf>.

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About Lilly Oncology

For more than fifty years, Lilly has been dedicated to delivering life-changing medicines and support to people living with cancer and those who care for them. Lilly is determined to build on this heritage and continue making life better for all those affected by cancer around the world. To learn more about Lilly's commitment to people with cancer, please visit

www.LillyOncology.com.

About Eli Lilly and Company

Lilly is a global healthcare leader that unites caring with discovery to make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at www.lilly.com and <http://newsroom.lilly.com/social-channels>.

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CYRAMZA[®] is a registered trademark of Eli Lilly and Company.

This press release contains forward-looking statements about the potential of CYRAMZA (ramucirumab) as a treatment of advanced gastric cancer and reflects Lilly's current beliefs. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. There can be no guarantee that future study results and patient experience will be consistent with the study findings to date. There can also be no guarantee that CYRAMZA will receive regulatory approval for any future indications or that it will prove to be commercially successful. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, please see the company's latest Forms 10-K and 10-Q filed with the U.S. Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements.

ⁱ Globocan 2012 Cancer Fact Sheet. Stomach cancer estimated incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed October 17, 2014.

ⁱⁱ American Cancer Society. What are the key statistics about stomach cancer? <http://www.cancer.org/Cancer/StomachCancer/DetailedGuide/stomach-cancer-key-statistics>. Updated May 27, 2014. Accessed October 17, 2014.

ⁱⁱⁱ Globocan 2012 Cancer Fact Sheet. Stomach cancer estimated incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed October 17, 2014.

^{iv} Globocan 2012 Cancer Fact Sheet. Stomach cancer estimated incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed October 17, 2014.

^v American Cancer Society. What are the key statistics about stomach cancer? <http://www.cancer.org/Cancer/StomachCancer/DetailedGuide/stomach-cancer-key-statistics>. Updated May 27, 2014. Accessed October 17, 2014.

^{vi} American Cancer Society. What is stomach cancer? <http://www.cancer.org/cancer/stomachcancer/detailedguide/stomach-cancer-what-is-stomach-cancer>. Updated May 27, 2014. Accessed October 17, 2014.

^{vii} American Cancer Society. What is stomach cancer? <http://www.cancer.org/cancer/stomachcancer/detailedguide/stomach-cancer-what-is-stomach-cancer>. Updated May 27, 2014. Accessed October 17, 2014.

^{viii} National Center for Biotechnology Information. Gastric cancer. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001270/>. Updated October 30, 2013. Accessed October 17, 2014.



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