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Lilly's CYRAMZA® (ramucirumab) Receives Third FDA Approval

CYRAMZA is the first treatment approved in the U.S. for use in combination with docetaxel in second-line metastatic non-small cell lung cancer

INDIANAPOLIS, Dec. 16, 2014 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) has received its third U.S. Food and Drug Administration (FDA) approval for CYRAMZA® (ramucirumab).

Specifically, CYRAMZA is now also indicated in combination with docetaxel, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA. This latest approval of CYRAMZA was received on December 12, 2014.

This approval of CYRAMZA (ramucirumab injection 10 mg/mL solution) marks the first FDA-approved medicine for use in combination with docetaxel in the second-line treatment of metastatic NSCLC, including nonsquamous and squamous histologies.

"Lilly is determined to meet the challenge of delivering new treatments for people with difficult-to-treat cancers, such as non-small cell lung cancer," said Sue Mahony, Ph.D., senior vice president and president, Lilly Oncology. "We are pleased with this approval and excited for the therapeutic advantage that CYRAMZA in combination with docetaxel can bring to second-line, metastatic NSCLC patients. It truly builds on Lilly's continued commitment to discovering potential treatment options for people fighting lung cancer."

The REVEL Phase III trial compared CYRAMZA plus docetaxel to placebo plus docetaxel, and included people with nonsquamous and squamous forms of NSCLC. 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.[i] 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.

Lung cancer is the leading cause of cancer death in the U.S. and most other countries, and NSCLC accounts for about 85 percent of all lung cancer cases.[ii,iii,iv] Approximately half of patients with metastatic NSCLC who begin first-line therapy will move on to second-line treatment.[v] Despite currently available therapies, there continues to be a need for new second-line treatment options for patients with NSCLC.[i]

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® (ramucirumab) is approved in combination with docetaxel (a type of chemotherapy) as a treatment for people with metastatic non-small cell lung cancer (NSCLC) whose cancer has progressed on or after platinum-based chemotherapy; it is also approved as a single agent or 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 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 REVEL
REVEL was a global, randomized, double-blinded Phase III study of CYRAMZA plus docetaxel compared to placebo plus docetaxel in people with metastatic NSCLC whose cancer had progressed on or after prior platinum-based chemotherapy for locally advanced or metastatic disease. In total, 1,253 patients - including people with nonsquamous (73%) and squamous (26%) forms of NSCLC - were randomized in 26 countries over six continents.[i] REVEL is the first positive Phase III study of a biologic in combination with chemotherapy to demonstrate improved overall survival compared to chemotherapy alone in second-line metastatic NSCLC.

In the trial, CYRAMZA plus docetaxel achieved a statistically significant improvement in overall survival (the primary endpoint), progression-free survival and objective response rate (secondary endpoints). CYRAMZA plus docetaxel significantly extended median overall survival compared to placebo plus docetaxel (10.5 months [95% confidence interval (CI): 9.5, 11.2] vs. 9.1 months [95% CI: 8.4, 10.0], respectively; hazard ratio 0.86 [95% CI: 0.75, 0.98]; *P*=0.024). Furthermore, CYRAMZA plus docetaxel significantly delayed disease progression (progression-free survival of 4.5 months for CYRAMZA plus docetaxel [95% CI: 4.2, 5.4] vs. 3.0 months for placebo plus docetaxel [95% CI: 2.8, 3.9]; hazard ratio 0.76 [95% CI: 0.68, 0.86]; $P < 0.001$). The percentage of deaths at the time of analysis was 68% (428 patients) and 73% (456 patients) in the CYRAMZA-plus-docetaxel and placebo-plus-docetaxel arms, respectively. The progression-free survival number of events was 558 (89%) and 583 (93%) for CYRAMZA-plus-docetaxel and placebo-plus-docetaxel treatment arms, respectively. Significantly more patients responded to CYRAMZA combined with docetaxel than with placebo plus docetaxel (23% [95% CI: 20, 26] for CYRAMZA plus docetaxel vs. 14% [95% CI: 11, 17] for placebo plus docetaxel; $P < 0.001$).

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 REVEL trial, the most common adverse reactions (all grades) observed in patients treated with CYRAMZA plus docetaxel at a rate of ≥30% and ≥2% higher than placebo were neutropenia (low white blood cell count) (55% vs. 46%), fatigue/asthenia (weakness) (55% vs. 50%) and stomatitis/mucosal inflammation (37% vs. 19%). The most common serious adverse events with CYRAMZA were febrile neutropenia (fever and potentially other infection signs along with low white blood cell count) (14%), pneumonia (6%), and neutropenia (5%); 42% of patients treated with CYRAMZA plus docetaxel received granulocyte colony-stimulating factors (treatment for low white blood cells) vs. 37% of patients who received placebo plus docetaxel. See the Important Safety Information at the end of this press release and the Prescribing Information.

About Lung Cancer
Lung cancer is the leading cause of cancer death in the U.S. and most other countries, killing nearly 1.6 million people worldwide each year.[ii] In the U.S., lung cancer is responsible for approximately 27 percent of all cancer deaths, more than those from breast, colon and prostate cancers combined.[iv] Stage IV NSCLC is a very difficult-to-treat cancer and the prognosis is poor for metastatic NSCLC.[vi] NSCLC is much more common than other types of lung cancer, and accounts for about 85 percent of all lung cancer cases. For those people affected by NSCLC, about 70 percent have nonsquamous cell carcinoma, while about 30 percent have squamous cell carcinoma.[iii] Approximately half of patients with metastatic NSCLC who begin first-line therapy will move on to second-line treatment.[v] Despite currently available therapies, there continues to be a need for new second-line treatment options for patients with NSCLC.[i]

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 (ramucirumab) is used with a chemotherapy called docetaxel to treat metastatic non-small cell lung cancer (NSCLC) in patients whose cancer has progressed on or after being treated with other initial types of chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

CYRAMZA is also approved as a single agent or 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.

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 in advanced gastric cancer, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroidal 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. In Study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from Study 3; therefore, the risk of pulmonary hemorrhage in these groups of patients 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%), in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%), and in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%). 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 advanced gastric cancer clinical trials experienced gastrointestinal perforation. In Study 2, the incidence of gastrointestinal perforation was 1.2% for CYRAMZA plus paclitaxel as compared to 0.3% for placebo plus paclitaxel. In Study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel as compared to 0.3% for placebo plus docetaxel. 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%).
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). 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 vs placebo 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).

Most Common Adverse Reactions—Combination With Docetaxel

- The most commonly reported adverse reactions (all grades; Grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus docetaxel and ≥2% higher than placebo plus docetaxel in Study 3 were neutropenia (55% vs 46%; 49% vs 40%), fatigue/asthenia (55% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%; < 1% vs < 1%), febrile neutropenia (16% vs 10%; 16% vs 10%), peripheral edema (16% vs 9%; 0% vs < 1%), thrombocytopenia (13% vs 5%; 3% vs < 1%), lacrimation increased (13% vs 5%; < 1% vs 0%), and hypertension (11% vs 5%; 6% vs 2%).
- The most common serious adverse events with CYRAMZA plus docetaxel in Study 3 were febrile neutropenia (14%),

pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel.
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA in Study 3 were infusion-related reaction (0.5%) and epistaxis (0.3%).
- Clinically relevant adverse reactions reported in ≥1% and < 5% of CYRAMZA plus docetaxel-treated patients in Study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

Drug Interactions

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

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.

For more information about CYRAMZA, including Boxed Warning for hemorrhage, please see full Prescribing Information 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 newsroom.lilly.com/social-channels.

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This press release contains forward-looking statements about the potential of CYRAMZA (ramucirumab) as a treatment of advanced non-small cell lung 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] Garon EB, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384:665-73.

[ii] International Agency for Research on Cancer. GLOBOCAN 2012. Lung Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr. Accessed December 2, 2014.

[iii] American Cancer Society. What is non-small cell lung cancer? http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-what-is-non-small-cell-lung-cancer. Updated November 10, 2014. Accessed December 2, 2014.

[iv] American Cancer Society. What are the key statistics about lung cancer? http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics. Updated November 10, 2014. Accessed December 2, 2014.

[v] Stinchcombe TE, Socinski MA. Considerations for Second-Line Therapy of Non-Small Cell Lung Cancer. *Oncologist*. 2008;13:28-36.

[vi] American Cancer Society. Learn about cancer: Non-small cell lung cancer survival rates by stage http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-survival-rates. Updated November 10, 2014. Accessed December 2, 2014.

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