April 24, 2015

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

CYRAMZA Now Approved in the U.S. for Use with FOLFIRI in Second-Line Treatment of Metastatic Colorectal Cancer

INDIANAPOLIS, April 24, 2015 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) has received its fourth U.S. Food and Drug Administration (FDA) approval for CYRAMZA® (ramucirumab). CYRAMZA (ramucirumab injection 10 mg/mL solution) is now also indicated in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil) chemotherapy for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

"CYRAMZA now has approvals in advanced or metastatic forms of three of the world's most common and deadly cancers - gastric, non-small cell lung, and colorectal - with four FDA approvals received in just over a year," said Sue Mahony, Ph.D., senior vice president and president, Lilly Oncology. "This progress is encouraging and supports our ongoing development program for CYRAMZA. Achieving today's milestone is another example of Lilly's commitment to people living with gastrointestinal cancers."

Dr. Mahony added, "We are also pleased with the efficient and collaborative reviews we had with the FDA on these submissions." While granted a standard review, this application for CYRAMZA in mCRC was reviewed and approved in approximately nine weeks following its submission to the FDA. All three supplemental applications for CYRAMZA received FDA approval within six months from the time of submission.

The approval is based on the Phase III trial known as RAISE, which compared CYRAMZA plus FOLFIRI to placebo plus FOLFIRI in people with mCRC who had disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Efficacy endpoints in the trial included the major efficacy outcome measure of overall survival (OS) and the supportive efficacy outcome measure of progression-free survival (PFS). The labeling for CYRAMZA contains Boxed Warnings for: hemorrhage, including severe and sometimes fatal events; gastrointestinal (GI) perforation, a potentially fatal event; and impaired wound healing. CYRAMZA should be permanently discontinued in patients who experience severe bleeding or a GI perforation. CYRAMZA should be withheld prior to surgery and discontinued if a patient develops wound healing complications. See the Important Safety Information at the end of this press release and the Prescribing Information.

For patients receiving CYRAMZA treatment, Lilly is committed to offering patient assistance programs. 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)
In the U.S., CYRAMZA (ramucirumab) is approved for use 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. It is also 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. Additionally, it is approved with FOLFIRI (a type of chemotherapy) as a therapy for people with metastatic colorectal cancer (mCRC) whose cancer has progressed on or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

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 and VEGF
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 and 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 the RAISE Trial
RAISE was a global, double-blind Phase III study of CYRAMZA plus FOLFIRI compared to placebo plus FOLFIRI as a second-line treatment for mCRC in patients who had disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Patients were randomized in a 1:1 ratio to receive CYRAMZA plus FOLFIRI (n=536) or placebo plus FOLFIRI (n=536) every two weeks.

In the RAISE trial, patients treated with the CYRAMZA-FOLFIRI combination achieved a median OS, the study's primary endpoint, of 13.3 months as compared to those treated with placebo-FOLFIRI who achieved 11.7 months, a statistically significant improvement that reduced the risk of patient death by 15 percent (HR 0.85; 95% CI: 0.73-0.98; p=0.023). The percentage of deaths at the time of analysis was 69 percent (372 patients) and 74 percent (397 patients) in the CYRAMZA-plus-FOLFIRI and placebo-plus-FOLFIRI treatment arms, respectively. The CYRAMZA combination also demonstrated a statistically significant improvement in the secondary endpoint of PFS over the placebo-FOLFIRI regimen, with a median PFS of 5.7 months vs. 4.5 months, respectively (HR 0.79; 95% CI: 0.70-0.90; p < 0.001). The percentage of events at the time of analysis was 89 percent (476 patients) and 92 percent (494 patients) in the CYRAMZA-plus-FOLFIRI and placebo-plus-FOLFIRI treatment arms, respectively. In the RAISE trial, randomization was stratified by geographic region, tumor KRAS status, and time to disease progression after beginning first-line treatment (< 6 months vs. ≥6 months). The treatment effect was consistent across the pre-specified stratification factors.

The labeling for CYRAMZA contains Boxed Warnings for hemorrhage, GI perforation, and impaired wound healing and additional Warnings and Precautions for arterial thromboembolic events, hypertension, infusion-related reactions, clinical deterioration in patients with Child-Pugh B or C cirrhosis, reversible posterior leukoencephalopathy syndrome, proteinuria including nephrotic syndrome, thyroid dysfunction, and embryofetal toxicity. The most common adverse reactions (all grades) observed in CYRAMZA-plus-FOLFIRI-treated patients at a rate of ≥30 percent and ≥2 percent higher than placebo plus FOLFIRI were diarrhea (60% vs. 51%), neutropenia (59% vs. 46%), decreased appetite (37% vs. 27%), epistaxis (33% vs. 15%), and stomatitis (31% vs. 21%). The most common serious adverse events with CYRAMZA plus FOLFIRI were diarrhea (3.6%), intestinal obstruction (3.0%), and febrile neutropenia (2.8%). See the Important Safety Information at the end of this press release and the Prescribing Information.

About Colorectal Cancer
Colorectal cancer (CRC) is a cancer that develops in the colon or the rectum, which are both parts of the gastrointestinal system. Metastatic CRC (mCRC) occurs when the disease has spread to at least one distant organ, such as the liver, lungs, or lining of the abdomen.

Despite advances in treating CRC in recent years, the mortality rate remains significant. CRC is the second leading cause of cancer death in the U.S. and fourth leading cause of cancer death worldwide, killing nearly 700,000 people in 2012.[i,ii,iii] The global incidence of CRC is estimated to be over 1.3 million.[i] Approximately one out of five CRC patients is diagnosed with metastatic disease, and the five-year survival rate for these patients is 12.9 percent.[iii]

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).

INDICATIONS
Gastric Cancer
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 (GEJ) adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.
Non-Small Cell Lung Cancer
CYRAMZA, in combination with docetaxel, is indicated 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.
Colorectal Cancer
CYRAMZA, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

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

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

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. In study 4, which evaluated CYRAMZA plus FOLFIRI in metastatic colorectal cancer, the incidence of severe bleeding was 2.5% for CYRAMZA plus FOLFIRI and 1.7% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, 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%), and in patients receiving CYRAMZA plus FOLFIRI (11%) as compared to placebo plus FOLFIRI (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 (IRRs)

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, 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. In study 4, the incidence of gastrointestinal perforation was 1.7% for CYRAMZA plus FOLFIRI and 0.6% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA, an antiangiogenic therapy, has 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.

Proteinuria Including Nephrotic Syndrome

- In study 4, severe proteinuria occurred more frequently in patients treated with CYRAMZA plus FOLFIRI compared to patients receiving placebo plus FOLFIRI. Severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases [0.6%] of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to < 2 g over 24 hours. Permanently discontinue CYRAMZA for urine protein levels > 3 g over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

- Monitor thyroid function during treatment with CYRAMZA. In study 4, the incidence of hypothyroidism reported as an adverse event was 2.6% in the CYRAMZA plus FOLFIRI-treated patients and 0.9% in the placebo plus FOLFIRI-treated patients.

Embryofetal Toxicity

- Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

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 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.
- In patients ≥65 years of age, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients < 65 years of age, there were 13 (3%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 26 (6%) deaths for 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%).
- For patients with nonsquamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of grade ≥3 pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of grade ≥3 pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 2% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel.
- 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).

Most Common Adverse Reactions—Combination With FOLFIRI

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus FOLFIRI and ≥2% higher than placebo plus FOLFIRI in study 4 were diarrhea (60% vs 51%; 11% vs 10%), neutropenia (59% vs 46%; 38% vs 23%), decreased appetite (37% vs 27%; 2% vs 2%), epistaxis (33% vs 15%; 0% vs 0%), and stomatitis (31% vs 21%; 4% vs 2%). Twenty percent of patients treated with CYRAMZA plus FOLFIRI received granulocyte colony-stimulating factors.
- The most common serious adverse events with CYRAMZA plus FOLFIRI were diarrhea (3.6%), intestinal obstruction (3.0%), and febrile neutropenia (2.8%).
- Treatment discontinuation of any study drug due to adverse reactions occurred more frequently in CYRAMZA plus FOLFIRI-treated patients (29%) than in placebo plus FOLFIRI-treated patients (13%). The most common adverse reactions leading to discontinuation of any component of CYRAMZA plus FOLFIRI as compared to placebo plus FOLFIRI, were neutropenia (12.5% versus 5.3%) and thrombocytopenia (4.2% versus 0.8%). The most common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (1.5%) and gastrointestinal perforation (1.7%).
- Clinically relevant adverse reactions reported in ≥1% and < 5% of CYRAMZA plus FOLFIRI-treated patients in study 4

consisted of gastrointestinal perforation (1.7% CYRAMZA plus FOLFIRI versus 0.6% for placebo plus FOLFIRI).
- Thyroid-stimulating hormone (TSH) was evaluated in 224 patients (115 CYRAMZA plus FOLFIRI-treated patients and 109 placebo plus FOLFIRI-treated patients) with normal baseline TSH levels. Patients received periodic TSH assessments until 30 days after the last dose of study treatment. Increased TSH was observed in 53 (46%) patients treated with CYRAMZA plus FOLFIRI compared with 4 (4%) patients treated with placebo plus FOLFIRI.

Drug Interactions

- No pharmacokinetic interactions were observed between ramucirumab and paclitaxel, between ramucirumab and docetaxel, or between ramucirumab and irinotecan or its active metabolite, SN-38.

Use in Specific Populations

- Pregnancy: Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA use in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and pediatric development, and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.
- Lactation: Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with CYRAMZA.
- Females of Reproductive Potential: Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Please see full Prescribing Information for CYRAMZA, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing.
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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. **(P-LLY)**

This press release contains forward-looking statements about the potential of CYRAMZA (ramucirumab) as a treatment of metastatic colorectal 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: Estimated Cancer Incidence, Mortality and Prevalence Worldwide, 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx (Accessed: April 22, 2015).

[ii] American Cancer Society, Cancer Facts & Figures 2015. Atlanta: American Cancer Society; 2015. http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf (Accessed: March 5, 2015).

[iii] National Cancer Institute, SEER 18 2004-2010, All Races, Both Sexes by SEER Summary Stage 2000. http://seer.cancer.gov/statfacts/html/colorect.html (Accessed: April 22, 2015).

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