HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CYRAMZA safely and effectively. See full prescribing information for CYRAMZA.

CYRAMZA (ramucirumab) injection, for intravenous use
Initial U.S. Approval: 2014

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

See full prescribing information for complete boxed warning.

- **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. (2.3, 5.1)**
- **Gastrointestinal Perforation: Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation. (2.3, 5.5)**
- **Impaired Wound Healing: Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications (2.3, 5.6)**

---------- RECENT MAJOR CHANGES ----------

Indications and Usage	
Gastric Cancer (1.1)	11/2014
Non-Small Cell Lung Cancer (1.2)	12/2014
Colorectal Cancer (1.3)	04/2015
Dosage and Administration:	
Recommended Dose and Schedule (2.1)	04/2015
Dose Modifications (2.3)	12/2014
Warnings and Precautions:	
Hemorrhage (5.1)	04/2015
Hypertension (5.3)	12/2014
Gastrointestinal Perforations (5.5)	04/2015
Impaired Wound Healing (5.6)	04/2015
Proteinuria Including Nephrotic Syndrome (5.9)	04/2015
Thyroid Dysfunction (5.10)	04/2015
Embryofetal Toxicity (5.11)	04/2015

---------- INDICATIONS AND USAGE ----------

CYRAMZA® is a human vascular endothelial growth factor receptor 2 antagonist indicated

- as a single agent or in combination with paclitaxel, for treatment of advanced gastric or gastro-esophageal junction adenocarcinoma, with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy. (1.1)
- in combination with docetaxel, for treatment of metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA. (1.2)
- in combination with FOLFIRI, for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. (1.3)

----------DOSAGE AND ADMINISTRATION----------

For intravenous infusion only. Do not administer as an intravenous push or bolus. (2)

Gastric Cancer
- The recommended dose of CYRAMZA either as a single agent or in combination with weekly paclitaxel is 8 mg/kg every 2 weeks. (2.1, 2.2, 2.3)

Non-Small Cell Lung Cancer
- Administer CYRAMZA at 10 mg/kg intravenously on day 1 of a 21-day cycle prior to docetaxel infusion. (2.1, 2.2, 2.3)

Colorectal Cancer
- Administer CYRAMZA at 8 mg/kg intravenously every 2 weeks, prior to FOLFIRI administration. (2.1, 2.2, 2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Injection:
- 100 mg/10 mL (10 mg per mL) solution, single-dose vial (3)
- 500 mg/50 mL (10 mg per mL) solution, single-dose vial (3)

---------- CONTRAINDICATIONS ----------

None (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Arterial Thromboembolic Events (ATEs): Serious, sometimes fatal ATEs have been reported in clinical trials. Discontinue CYRAMZA for severe ATEs. (5.2)
- Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend CYRAMZA for severe hypertension. Discontinue CYRAMZA for hypertension that cannot be medically controlled. (5.3)
- Infusion-Related Reactions: Monitor for signs and symptoms during infusion. (5.4)
- Impaired Wound Healing: Withhold CYRAMZA prior to surgery. (5.6)
- Clinical Deterioration in Patients with Cirrhosis: New onset or worsening encephalopathy, ascites, or hepatorenal syndrome can occur in patients with Child-Pugh B or C cirrhosis. (5.7)
- Reversible Posterior Leukoencephalopathy Syndrome: Discontinue CYRAMZA. (5.8)
- Proteinuria Including Nephrotic Syndrome: Monitor proteinuria. Interrupt CYRAMZA for urine protein levels ≥2 g/24 hours. Permanently discontinue CYRAMZA for urine protein levels >3 g/24 hours or for nephrotic syndrome. (5.9)
- Thyroid Dysfunction: Monitor thyroid function during treatment with CYRAMZA. (5.10)
- Embryofetal Risk: Can cause fetal harm. (5.11)

---------- ADVERSE REACTIONS ----------
- The most common adverse reactions observed in single-agent CYRAMZA-treated patients at a rate of ≥10% and ≥2% higher than placebo were hypertension and diarrhea. (6.1)
- The most common adverse reactions observed in patients treated with CYRAMZA plus paclitaxel at a rate of ≥30% and ≥2% higher than placebo plus paclitaxel were fatigue, neutropenia, diarrhea, and epistaxis. (6.1)
- The most common adverse reactions observed in patients treated with CYRAMZA plus docetaxel at a rate of ≥30% and ≥2% higher than placebo plus docetaxel were neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation. (6.1)
- The most common adverse reactions observed in patients treated with CYRAMZA plus FOLFIRI at a rate of ≥30% and ≥2% higher than placebo plus FOLFIRI were diarrhea, neutropenia, decreased appetite, epistaxis, and stomatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Breastfeeding is not advised. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 *[see Dosage and Administration (2.3), Warnings and Precautions (5.1)]*.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation *[see Dosage and Administration (2.3), Warnings and Precautions (5.5)].*

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 *[see Dosage and Administration (2.3), Warnings and Precautions (5.6)].*

1 INDICATIONS AND USAGE

1.1 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 gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

1.2 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 EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

1.3 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.

2 DOSAGE AND ADMINISTRATION

Do not administer CYRAMZA as an intravenous push or bolus.

2.1 Recommended Dose and Schedule

Gastric Cancer

- The recommended dose of CYRAMZA either as a single agent or in combination with weekly paclitaxel is 8 mg/kg every 2 weeks administered as an intravenous infusion over 60 minutes. Continue CYRAMZA until disease progression or unacceptable toxicity.
- When given in combination, administer CYRAMZA prior to administration of paclitaxel.

Non-Small Cell Lung Cancer

- The recommended dose of CYRAMZA is 10 mg/kg administered by intravenous infusion over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion. Continue CYRAMZA until disease progression or unacceptable toxicity.

Colorectal Cancer

- The recommended dose of CYRAMZA is 8 mg/kg every 2 weeks administered by intravenous infusion over 60 minutes prior to FOLFIRI administration. Continue CYRAMZA until disease progression or unacceptable toxicity.

2.2 Premedication

- Prior to each CYRAMZA infusion, premedicate all patients with an intravenous histamine H_1 antagonist (e.g., diphenhydramine hydrochloride).

- For patients who have experienced a Grade 1 or 2 infusion-related reaction, also premedicate with dexamethasone (or equivalent) and acetaminophen prior to each CYRAMZA infusion *[see Dosage and Administration (2.3)]*.

2.3 Dose Modifications

Infusion-Related Reactions (IRR)

- Reduce the infusion rate of CYRAMZA by 50% for Grade 1 or 2 IRRs.
- Permanently discontinue CYRAMZA for Grade 3 or 4 IRRs *[see Dosage and Administration (2.2) and Warnings and Precautions (5.4)]*.

Hypertension

- Interrupt CYRAMZA for severe hypertension until controlled with medical management.
- Permanently discontinue CYRAMZA for severe hypertension that cannot be controlled with antihypertensive therapy *[see Warnings and Precautions (5.3)]*.

Proteinuria

- Interrupt CYRAMZA for urine protein levels ≥2 g/24 hours. Reinitiate treatment at a reduced dose (see Table 1) once the urine protein level returns to <2 g/24 hours. If the protein level ≥2 g/24 hours reoccurs, interrupt CYRAMZA and reduce the dose (see Table 1) once the urine protein level returns to <2 g/24 hours.
- Permanently discontinue CYRAMZA for urine protein level >3 g/24 hours or in the setting of nephrotic syndrome *[see Warnings and Precautions (5.9) and Adverse Reactions (6.1)]*.

Table 1: CYRAMZA Dose Reductions for Proteinuria

Initial CYRAMZA Dose	First Dose Reduction to:	Second Dose Reduction to:
8 mg/kg	6 mg/kg	5 mg/kg
10 mg/kg	8 mg/kg	6 mg/kg

Wound Healing Complications

- Interrupt CYRAMZA prior to scheduled surgery until the wound is fully healed *[see Warnings and Precautions (5.6)]*.

Arterial Thromboembolic Events, Gastrointestinal Perforation, or Grade 3 or 4 Bleeding

- Permanently discontinue CYRAMZA *[see Warnings and Precautions (5.1, 5.2, 5.5)]*.

For toxicities related to paclitaxel, docetaxel, or the components of FOLFIRI, refer to the current prescribing information.

2.4 Preparation for Administration

Inspect vial contents for particulate matter and discoloration prior to dilution *[see Description (11)]*. Discard the vial, if particulate matter or discolorations are identified. Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light.

- Calculate the dose and the required volume of CYRAMZA needed to prepare the infusion solution. Vials contain either 100 mg/10 mL or 500 mg/50 mL at a concentration of 10 mg/mL solution of CYRAMZA.
- Withdraw the required volume of CYRAMZA and further dilute with only 0.9% Sodium Chloride Injection in an intravenous infusion container to a final volume of 250 mL. Do not use dextrose containing solutions.
- Gently invert the container to ensure adequate mixing.
- **DO NOT FREEZE OR SHAKE** the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications.
- Store diluted infusion for no more than 24 hours at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature (below 25°C [77°F]).
- Discard vial with any unused portion of CYRAMZA.

2.5 Administration

- Visually inspect the diluted solution for particulate matter and discoloration prior to administration. If particulate matter or discolorations are identified, discard the solution.
- Administer diluted CYRAMZA infusion via infusion pump over 60 minutes through a separate infusion line. Use of a protein sparing 0.22 micron filter is recommended. Flush the line with sterile sodium chloride (0.9%) solution for injection at the end of the infusion.

3 DOSAGE FORMS AND STRENGTHS

Injection:

- 100 mg/10 mL (10 mg per mL) solution, single-dose vial
- 500 mg/50 mL (10 mg per mL) solution, single-dose vial

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In Study 1, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In Study 2, 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, 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 anti-platelet 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, 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 *[see Dosage and Administration (2.3)]*.

5.2 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 *[see Dosage and Administration (2.3)]*.

5.3 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%), 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 two 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 *[see Dosage and Administration (2.3)]*.

5.4 Infusion-Related Reactions

Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including two 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 *[see Dosage and Administration (2.3)]*.

5.5 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 perforation was also increased in patients that received CYRAMZA plus paclitaxel (1.2%) as compared to patients receiving placebo plus paclitaxel (0.3%). In Study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel and 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 *[see Dosage and Administration (2.3)]*.

5.6 Impaired Wound Healing

Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or non-healing wounds. CYRAMZA, an antiangiogenic therapy, has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing.

Withhold CYRAMZA prior to surgery. Resume 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 *[see Dosage and Administration (2.3)]*.

5.7 Clinical Deterioration in Patients with 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.

5.8 Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported with 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.

5.9 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 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome *[see Dosage and Administration (2.3)].*

5.10 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.

5.11 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 3 least months after the last dose of CYRAMZA *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse drug reactions are discussed in greater detail in other sections of the label:

- Hemorrhage *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.
- Arterial Thromboembolic Events *[see Dosage and Administration (2.3) and Warnings and Precautions (5.2)]*.
- Hypertension *[see Dosage and Administration (2.3) and Warnings and Precautions (5.3)]*.
- Infusion-Related Reactions *[see Dosage and Administration (2.3) and Warnings and Precautions (5.4)]*.
- Gastrointestinal Perforation *[see Dosage and Administration (2.3) and Warnings and Precautions (5.5)]*.
- Impaired Wound Healing *[see Dosage and Administration (2.3) and Warnings and Precautions (5.6)]*.
- Patients with Child-Pugh B or C Cirrhosis *[see Warnings and Precautions (5.7)]*.
- Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.8)]*.
- Proteinuria Including Nephrotic Syndrome *[see Warnings and Precautions (5.9)]*.
- Thyroid Dysfunction *[see Warnings and Precautions (5.10)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Gastric Cancer

Safety data are presented from two randomized, placebo controlled clinical trials in which patients received CYRAMZA: Study 1, a randomized (2:1), double-blind, clinical trial in which 351 patients received either CYRAMZA 8 mg/kg intravenously every two weeks or placebo every two weeks and Study 2, a double-blind, randomized (1:1) clinical trial in which 656 patients received paclitaxel 80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle plus either CYRAMZA 8 mg/kg intravenously every two weeks or placebo every two weeks. Both trials excluded patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or greater, uncontrolled hypertension, major surgery within 28 days, or patients receiving chronic anti-platelet therapy other than once daily aspirin. Study 1 excluded patients with bilirubin ≥1.5 mg/dL and Study 2 excluded patients with bilirubin >1.5 times the upper limit of normal.

CYRAMZA Administered as a Single Agent

Among 236 patients who received CYRAMZA (safety population) in Study 1, median age was 60 years, 28% were women, 76% were White, and 16% were Asian. Patients in Study 1 received a median of 4 doses of CYRAMZA; the median duration of exposure was 8 weeks, and 32 (14% of 236) patients received CYRAMZA for at least six months.

In Study 1, the most common adverse reactions (all grades) observed in CYRAMZA-treated patients at a rate of ≥10% and ≥2% higher than placebo were hypertension and diarrhea. The most common serious adverse events with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients versus 8.7% of patients who received placebo.

Table 2 provides the frequency and severity of adverse reactions in Study 1.

Table 2: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 1

Adverse Reactions (MedDRA) System Organ Class	CYRAMZA (8 mg/kg) N=236		Placebo N=115	
	All Grades (Frequency %)	Grade 3-4 (Frequency %)	All Grades (Frequency %)	Grade 3-4 (Frequency %)
Gastrointestinal Disorders				
Diarrhea	14	1	9	2
Metabolism and Nutrition Disorders				
Hyponatremia	6	3	2	1
Nervous System Disorders				
Headache	9	0	3	0
Vascular Disorders				
Hypertension	16	8	8	3

Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in Study 1 were: neutropenia (4.7% CYRAMZA versus 0.9% placebo), epistaxis (4.7% CYRAMZA versus 0.9% placebo), rash (4.2% CYRAMZA versus 1.7% placebo), intestinal obstruction (2.1% CYRAMZA versus 0% placebo), and arterial

thromboembolic events (1.7% CYRAMZA versus 0% placebo) *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1, 5.2)]*.

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 versus 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% *[see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.4, 5.5)]*.

CYRAMZA Administered in Combination with Paclitaxel

Among 327 patients who received CYRAMZA (safety population) in Study 2, median age was 61 years, 31% were women, 63% were White, and 33% were Asian. Patients in Study 2 received a median of 9 doses of CYRAMZA; the median duration of exposure was 18 weeks, and 93 (28% of 327) patients received CYRAMZA for at least six months.

In Study 2, the most common adverse reactions (all grades) observed in patients treated with CYRAMZA plus paclitaxel at a rate of ≥30% and ≥2% higher than placebo plus paclitaxel were fatigue, neutropenia, diarrhea, and epistaxis. The most common serious adverse events with CYRAMZA plus paclitaxel 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%).

Table 3 provides the frequency and severity of adverse reactions in Study 2.

Table 3: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA plus Paclitaxel in Study 2

Adverse Reactions (MedDRA) System Organ Class	CYRAMZA plus Paclitaxel (N=327)		Placebo plus Paclitaxel (N=329)	
	All Grades (Frequency %)	Grade ≥3 (Frequency %)	All Grades (Frequency %)	Grade ≥3 (Frequency %)
Blood and Lymphatic System Disorders				
Neutropenia	54	41	31	19
Thrombocytopenia	13	2	6	2
Gastrointestinal Disorders				
Diarrhea	32	4	23	2
Gastrointestinal hemorrhage events	10	4	6	2
Stomatitis	20	1	7	1
General Disorders and Administration Site Disorders				
Fatigue/Asthenia	57	12	44	6
Peripheral edema	25	2	14	1
Metabolism and Nutrition Disorders				
Hypoalbuminemia	11	1	5	1
Renal and Urinary Disorders				
Proteinuria	17	1	6	0
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	31	0	7	0
Vascular Disorder				
Hypertension	25	15	6	3

Clinically relevant adverse reactions reported in ≥1% and <5% of the CYRAMZA plus paclitaxel treated patients in Study 2 were sepsis (3.1% CYRAMZA plus paclitaxel versus 1.8% placebo plus paclitaxel) and gastrointestinal perforations (1.2% CYRAMZA plus paclitaxel versus 0.3% for placebo plus paclitaxel).

Non-Small Cell Lung Cancer

CYRAMZA Administered in Combination with Docetaxel

Study 3 was a multinational, randomized, double-blind study conducted in patients with NSCLC with disease progression on or after one platinum-based therapy for locally advanced or metastatic disease. Patients received either CYRAMZA 10 mg/kg intravenously plus docetaxel 75 mg/m^2 intravenously every 3 weeks or placebo plus docetaxel 75 mg/m^2 intravenously every 3 weeks. Due to an increased incidence of neutropenia and febrile neutropenia in patients

enrolled in East Asian sites, Study 3 was amended and 24 patients (11 CYRAMZA plus docetaxel, 13 placebo plus docetaxel) at East Asian sites received a starting dose of docetaxel at 60 mg/m^2 every 3 weeks.

Study 3 excluded patients with an ECOG PS of 2 or greater, bilirubin greater than the upper limit of normal (ULN), uncontrolled hypertension, major surgery within 28 days, radiographic evidence of major airway or blood vessel invasion by cancer, radiographic evidence of intra-tumor cavitation, or gross hemoptysis within the preceding 2 months, and patients receiving therapeutic anticoagulation or chronic anti-platelet therapy other than once daily aspirin. The study also excluded patients whose only prior treatment for advanced NSCLC was a tyrosine kinase (epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK]) inhibitor.

The data described below reflect exposure to CYRAMZA plus docetaxel in 627 patients in Study 3. Demographics and baseline characteristics were similar between treatment arms. Median age was 62 years; 67% of patients were men; 84% were White and 12% were Asian; 33% had ECOG PS 0; 74% had non-squamous histology and 25% had squamous histology. Patients received a median of 4.5 doses of CYRAMZA; the median duration of exposure was 3.5 months, and 195 (31% of 627) patients received CYRAMZA for at least six months.

In Study 3, the most common adverse reactions (all grades) observed in CYRAMZA plus docetaxel-treated patients at a rate of ≥30% and ≥2% higher than placebo plus docetaxel were neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation. 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 were infusion-related reaction (0.5%) and epistaxis (0.3%). For patients with non-squamous 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.

The most common serious adverse events with CYRAMZA plus docetaxel 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, 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, 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.

Table 4 provides the frequency and severity of adverse reactions in Study 3.

Table 4: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 3

Adverse Reactions (MedDRA) System Organ Class	CYRAMZA plus docetaxel (N=627)		Placebo plus docetaxel (N=618)	
	All Grades (Frequency %)	Grade 3-4 (Frequency %)	All Grades (Frequency %)	Grade 3-4 (Frequency %)
Blood and Lymphatic System Disorders				
Febrile neutropenia	16	16	10	10
Neutropenia	55	49	46	40
Thrombocytopenia	13	3	5	<1
Gastrointestinal Disorders				
Stomatitis/Mucosal inflammation	37	7	19	2
Eye Disorders				
Lacrimation increased	13	<1	5	0
General Disorders and Administration Site Disorders				
Fatigue/Asthenia	55	14	50	11
Peripheral edema	16	0	9	<1
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	19	<1	7	<1
Vascular Disorders				
Hypertension	11	6	5	2

Clinically relevant adverse drug reactions reported in ≥1% and <5% of the 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).

Colorectal Cancer

CYRAMZA Administered in Combination with FOLFIRI

Study 4 was a multinational, randomized, double-blind study conducted in patients with metastatic colorectal cancer with disease progression on or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Patients received either CYRAMZA 8 mg/kg intravenously plus FOLFIRI intravenously every 2 weeks or placebo plus FOLFIRI intravenously every 2 weeks.

Study 4 excluded patients with an ECOG PS of 2 or greater, uncontrolled hypertension, major surgery within 28 days, and those who experienced any of the following during first-line therapy with a bevacizumab-containing regimen: an arterial thrombotic/thromboembolic event; Grade 4 hypertension; Grade 3 proteinuria; a Grade 3-4 bleeding event; or bowel perforation.

Demographics and baseline characteristics for the treated population were similar between treatment arms (n=1057). Median age was 62 years; 57% of patients were men; 76% were White and 20% were Asian; 48% had ECOG PS 0.

The data described in this section reflect exposure to CYRAMZA plus FOLFIRI in 529 patients in Study 4. Patients received a median of 8 doses (range 1-68) of CYRAMZA; the median duration of exposure was 4.4 months, and 169 (32% of 529) patients received CYRAMZA for at least six months. The most common adverse reactions (all grades) observed in CYRAMZA plus FOLFIRI-treated patients at a rate of ≥30% and ≥2% higher than placebo plus FOLFIRI were diarrhea, neutropenia, decreased appetite, epistaxis, and stomatitis. Twenty percent of patients treated with CYRAMZA plus FOLFIRI received granulocyte colony-stimulating factors. 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%).

The most common serious adverse events with CYRAMZA plus FOLFIRI were diarrhea (3.6%), intestinal obstruction (3.0%), and febrile neutropenia (2.8%).

Table 5 provides the frequency and severity of adverse reactions in Study 4.

Table 5: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 4

Adverse Reactions (MedDRA) System Organ Class	CYRAMZA plus FOLFIRI N=529		Placebo plus FOLFIRI N=528	
	All Grades (Frequency %)	Grade ≥3 (Frequency %)	All Grades (Frequency %)	Grade ≥3 (Frequency %)
Blood and Lymphatic System Disorders				
Neutropenia	59	38	46	23
Thrombocytopenia	28	3	14	<1
Gastrointestinal Disorders				
Decreased appetite	37	2	27	2
Diarrhea	60	11	51	10
Gastrointestinal hemorrhage events	12	2	7	1
Stomatitis	31	4	21	2
General Disorders and Administration Site Disorders				
Peripheral edema	20	<1	9	0
Metabolism and Nutrition Disorders				
Hypoalbuminemia	6	1	2	0
Renal and Urinary Disorders				
Proteinuria[a]	17	3	5	<1
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	33	0	15	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia syndrome	13	1	5	<1
Vascular Disorders				
Hypertension	26	11	9	3

[a] Includes 3 patients with nephrotic syndrome in the CYRAMZA plus FOLFIRI treatment group.

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) levels were evaluated in 224 patients (115 CYRAMZA plus FOLFIRI-treated patients and 109 placebo plus FOLFIRI-treated patients) with normal baseline TSH levels. Patients underwent periodic TSH laboratory assessments until 30 days after the last dose of study treatment. Increased TSH levels were observed in 53 (46%) patients treated with CYRAMZA plus FOLFIRI compared with 4 (4%) patients treated with placebo plus FOLFIRI.

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In 23 clinical trials, 86/2890 (3.0%) of CYRAMZA-treated patients tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 14 of the 86 patients who tested positive for treatment-emergent anti-ramucirumab antibodies.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to CYRAMZA with the incidences of antibodies to other products may be misleading.

7 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 *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1)]*, 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. The background risk of major birth defects and miscarriage for the indicated populations are unknown. In the U.S. general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Advise pregnant women of the potential risk to a fetus.

Data

Animal Data

No animal studies have been specifically conducted to evaluate the effect of ramucirumab on reproduction and fetal development. In mice, loss of the VEGFR2 gene resulted in embryofetal death and these fetuses lacked organized blood vessels and blood islands in the yolk sac. In other models, VEGFR2 signaling was associated with development and maintenance of endometrial and placental vascular function, successful blastocyst implantation, maternal and feto-placental vascular differentiation, and development during early pregnancy in rodents and non-human primates. Disruption of VEGF signaling has also been associated with developmental anomalies including poor development of the cranial region, forelimbs, forebrain, heart, and blood vessels.

8.2 Lactation

Risk Summary

There is no information on the presence of ramucirumab in human milk, the effects on the breast-fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. 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.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action, CYRAMZA can cause fetal harm *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception while receiving CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Infertility

Females

Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of CYRAMZA in pediatric patients have not been established. In animal studies, effects on epiphyseal growth plates were identified. In cynomolgus monkeys, anatomical pathology revealed adverse effects on the epiphyseal growth plate (thickening and osteochondropathy) at all doses tested (5-50 mg/kg). Ramucirumab exposure at the lowest weekly dose tested in the cynomolgus monkey was 0.2 times the exposure in humans at the recommended dose of ramucirumab as a single agent.

8.5 Geriatric Use

Of the 563 CYRAMZA-treated patients in two randomized gastric cancer clinical studies, 36% were 65 and over, while 7% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. *[see Clinical Studies (14.1)]*

Of the 1253 patients in Study 3, 455 (36%) were 65 and over and 84 (7%) were 75 and over. Of the 627 patients who received CYRAMZA plus docetaxel in Study 3, 237 (38%) were 65 and over, while 45 (7%) were 75 and over *[see Clinical Studies (14.2)]*. In an exploratory subgroup analysis of Study 3, the hazard ratio for overall survival in patients less than 65 years old was 0.74 (95% CI: 0.62, 0.87) and in patients 65 years or older was 1.10 (95% CI: 0.89, 1.36). *[see Clinical Studies (14.2)]*

Of the 529 patients who received CYRAMZA plus FOLFIRI in Study 4, 209 (40%) were 65 and over, while 51 (10%) were 75 and over. Overall, no differences in safety or effectiveness were observed between these subjects and younger subjects. *[see Clinical Studies (14.3)]*

8.6 Renal Impairment

No dose adjustment is recommended for patients with renal impairment based on population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild (total bilirubin within upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN, or total bilirubin >1.0-1.5 times ULN and any AST) or moderate (total bilirubin >1.5-3.0 times ULN and any AST) hepatic impairment based on population pharmacokinetic analysis. Clinical deterioration was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA *[see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There are no data on overdose in humans. CYRAMZA was administered at doses up to 10 mg/kg every two weeks without reaching a maximum tolerated dose.

11 DESCRIPTION

CYRAMZA (ramucirumab) is a recombinant human IgG1 monoclonal antibody that specifically binds to vascular endothelial growth factor receptor 2. CYRAMZA has an approximate molecular weight of 147 kDa. CYRAMZA is produced in genetically engineered mammalian NS0 cells.

CYRAMZA is a sterile, preservative-free, clear to slightly opalescent and colorless to slightly yellow solution for intravenous infusion following dilution and preparation. CYRAMZA is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-dose vials. CYRAMZA is formulated in glycine (9.98 mg/mL), histidine (0.65 mg/mL), histidine monohydrochloride (1.22 mg/mL), polysorbate 80 (0.1 mg/mL), sodium chloride (4.383 mg/mL), and Water for Injection, USP, pH 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ramucirumab is a vascular endothelial growth factor receptor 2 antagonist that specifically binds VEGF Receptor 2 and blocks binding of VEGFR ligands, VEGF-A, VEGF-C, and VEGF-D. As a result, ramucirumab inhibits ligand-stimulated activation of VEGF Receptor 2, thereby inhibiting ligand-induced proliferation, and migration of human endothelial cells. Ramucirumab inhibited angiogenesis in an in vivo animal model.

12.3 Pharmacokinetics

The pharmacokinetic (PK) characteristics of ramucirumab are similar for patients with gastric cancer, NSCLC, and mCRC based on a population PK analysis. The mean (% coefficient of variation [CV%]) clearance for ramucirumab was 0.015 L/hour (30%) and the mean terminal half-life was 14 days (20%).

Specific Populations

Age, sex, and race had no clinically meaningful effect on the PK of ramucirumab based on a population PK analysis.

Renal Impairment: Based on a population PK analysis, no clinically meaningful differences in the average concentration of ramucirumab at steady state (C_{ss}) were observed in patients with mild (calculated creatinine clearance [CLcr] 60-89 mL/min, n=687), moderate (CLcr 30-59 mL/min, n=244) or severe (CLcr 15-29 mL/min, n=6) renal impairment compared to patients with normal renal function (CLcr ≥90 mL/min, n=697).

Hepatic Impairment: Based on a population PK analysis, no clinically meaningful differences in the average C_{ss} of ramucirumab were observed in patients with mild (total bilirubin within upper limit of normal [ULN] and AST>ULN, or total bilirubin >1.0-1.5 times ULN and any AST, n=525), or moderate (total bilirubin >1.5-3.0 times ULN n=23) hepatic impairment compared to patients with normal hepatic function (total bilirubin and AST ≤ULN, n=1055). No PK data are available from patients with severe hepatic dysfunction (total bilirubin >3.0 times ULN and any AST).

Drug Interaction Studies

No clinically meaningful changes in the exposure of either ramucirumab or its concomitant drugs in the approved combinations, including paclitaxel, docetaxel, and irinotecan (or its active metabolite, SN-38), were observed in patients with solid tumors.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been performed to test ramucirumab for potential carcinogenicity or genotoxicity.

Inhibition of VEGFR2 signaling in animal models was shown to result in changes to hormone levels critical for pregnancy, and, in monkeys, an increased duration of the follicular cycle. In a 39 week animal study, female monkeys treated with ramucirumab showed dose dependent increases in follicular mineralization of the ovary.

13.2 Animal Toxicology and/or Pharmacology

Adverse effects in the kidney (glomerulonephritis) occurred in monkeys at doses of 16-50 mg/kg (0.7-5.5 times the exposure in humans at the recommended dose of ramucirumab as a single agent).

A single dose of ramucirumab resulting in an exposure approximately 10 times the exposure in humans at the recommended dose of ramucirumab as a single agent did not significantly impair wound healing in monkeys using a full-thickness incisional model.

14 CLINICAL STUDIES

14.1 Gastric Cancer

Study 1 was a multinational, randomized, double-blind, multicenter study of CYRAMZA plus best supportive care (BSC) versus placebo plus BSC that randomized (2:1) 355 patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the gastro-esophageal junction [GEJ]) who previously received platinum- or fluoropyrimidine-containing chemotherapy. The major efficacy outcome measure was overall survival and the supportive efficacy outcome measure was progression-free survival. Patients were required to have experienced disease progression either within 4 months after the last dose of first-line therapy for locally advanced or metastatic disease or within 6 months after the last dose of adjuvant therapy. Patients were also required to have ECOG PS of 0 or 1. Patients received either an intravenous infusion of CYRAMZA 8 mg/kg (n=238) or placebo solution (n=117) every 2 weeks. Randomization was stratified by weight loss over the prior 3 months (≥10% versus <10%), geographic region, and location of the primary tumor (gastric versus GEJ).

Demographic and baseline characteristics were similar between treatment arms. Median age was 60 years; 70% of patients were men; 77% were White, 16% Asian; the ECOG PS was 0 for 28% of patients and 1 for 72% of patients; 91% of patients had measurable disease; 75% of patients had gastric cancer; and 25% had adenocarcinoma of the GEJ. The majority of patients (85%) experienced disease progression during or following first-line therapy for metastatic disease. Prior chemotherapy for gastric cancer consisted of platinum/fluoropyrimidine combination therapy (81%), fluoropyrimidine-containing regimens without platinum (15%), and platinum-containing regimens without fluoropyrimidine (4%). In Study 1, patients received a median of 4 doses (range 1-34) of CYRAMZA or a median of 3 doses (range 1-30) of placebo.

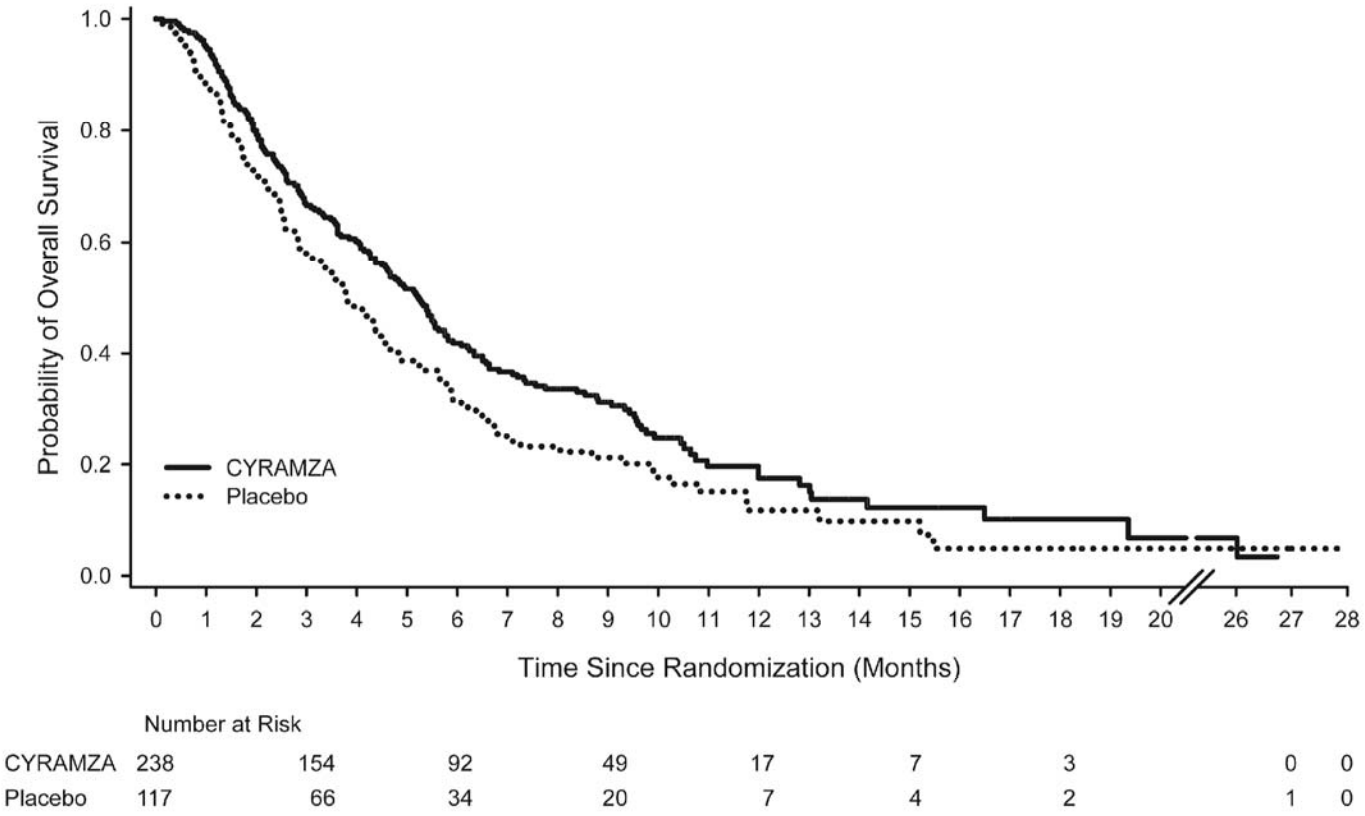
Overall survival and progression-free survival were statistically significantly improved in patients randomized to receive CYRAMZA as compared to patients randomized to receive placebo. Efficacy results are shown in Table 6 and Figure 1.

Table 6: Randomized Trial of CYRAMZA plus BSC versus Placebo plus BSC in Gastric Cancer

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

Abbreviations: CI = confidence interval

Figure 1: Kaplan-Meier Curves of Overall Survival - CYRAMZA plus BSC versus Placebo plus BSC in Gastric Cancer



Study 2 was a multinational, randomized, double-blind study of CYRAMZA plus paclitaxel versus placebo plus paclitaxel that randomized (1:1) 665 patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the gastro-esophageal junction) who previously received platinum- and fluoropyrimidine-containing chemotherapy. Patients were required to have experienced disease progression during, or within 4 months after the last dose of first-line therapy. Patients were also required to have ECOG PS of 0 or 1. Randomization was stratified by geographic region, time to progression from the start of first-line therapy (<6 months versus ≥6 months) and disease measurability.

Patients were randomized to receive either CYRAMZA 8 mg/kg (n=330) or placebo (n=335) as an intravenous infusion every 2 weeks (on days 1 and 15) of each 28-day cycle. Patients in both arms received paclitaxel 80 mg/m^2 by intravenous infusion on days 1, 8, and 15 of each 28-day cycle. Prior to administration of each dose of paclitaxel, patients were required to have adequate hematopoietic and hepatic function. The paclitaxel dose was permanently reduced in increments of 10 mg/m^2 for a maximum of two dose reductions for Grade 4 hematologic toxicity or Grade 3 paclitaxel-

related non-hematologic toxicity. The major efficacy outcome measure was overall survival and the supportive efficacy outcome measures were progression-free survival and objective response rate.

Demographics and baseline characteristics were similar between treatment arms including the following: Median age was 61 years; 71% of patients were men; 61% were White, 35% Asian; the ECOG PS was 0 for 39% of patients, 1 for 61% of patients; 78% of patients had measurable disease; 79% of patients had gastric cancer; and 21% had adenocarcinoma of the GEJ. Two-thirds of the patients experienced disease progression while on first-line therapy (67%) and 25% of patients received an anthracycline in combination with platinum/fluoropyrimidine combination therapy.

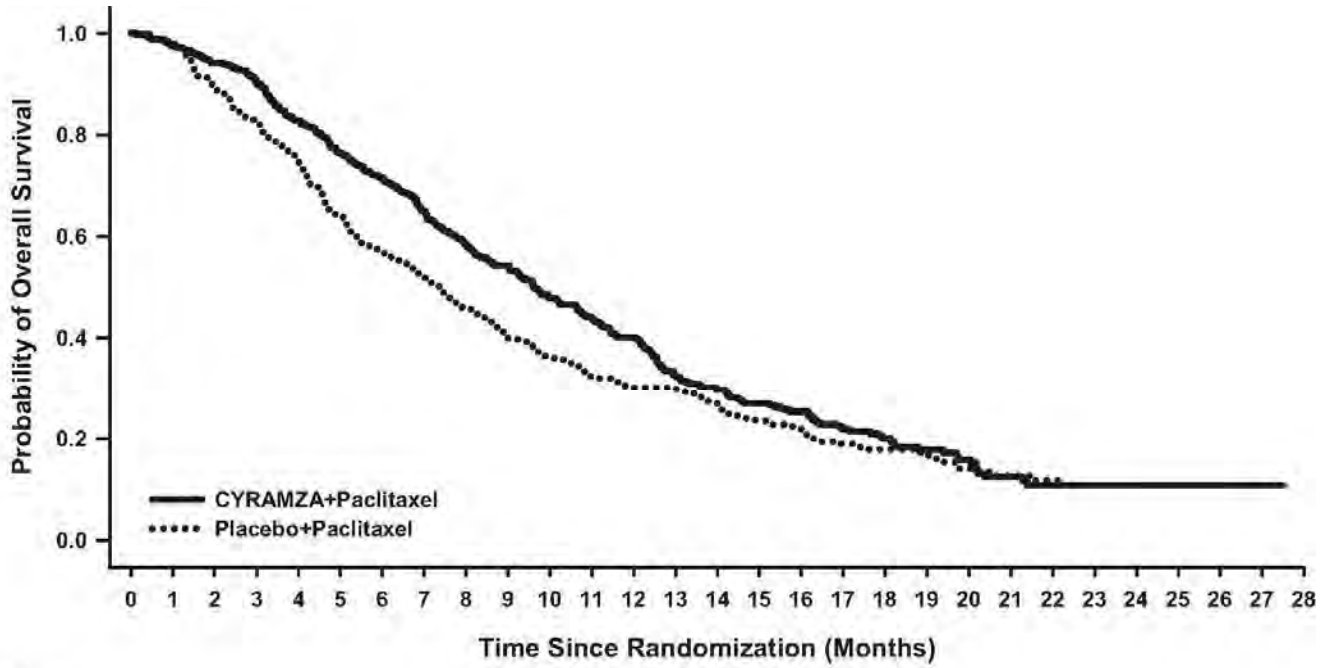
Overall survival, progression-free survival, and objective response rate were statistically significantly improved in patients randomized to receive CYRAMZA plus paclitaxel compared to patients randomized to receive placebo plus paclitaxel. Efficacy results are shown in Table 7 and Figure 2.

Table 7: Randomized Trial of CYRAMZA plus Paclitaxel versus Placebo plus Paclitaxel in Gastric Cancer

	CYRAMZA + paclitaxel N=330	**Placebo + paclitaxel N=335**
Overall Survival		
Number of deaths (%)	256 (78%)	260 (78%)
Median – months (95% CI)	9.6 (8.5, 10.8)	7.4 (6.3, 8.4)
Hazard Ratio (95% CI)	0.81 (0.68, 0.96)	
Stratified Log-rank p-value	0.017	
Progression-free Survival		
Number of events (%)	279 (85%)	296 (88%)
Median – months (95% CI)	4.4 (4.2, 5.3)	2.9 (2.8, 3.0)
Hazard Ratio (95% CI)	0.64 (0.54, 0.75)	
Stratified Log-rank p-value	<0.001	
Objective Response Rate (CR + PR)		
Rate – percent (95% CI)	28 (23, 33)	16 (13, 20)
Stratified CMH p-value	<0.001	

Abbreviations: CI = confidence interval, CR = complete response, PR = partial response, CMH = Cochran-Mantel-Haenszel

Figure 2: Kaplan-Meier Curves of Overall Survival - CYRAMZA plus Paclitaxel versus Placebo plus Paclitaxel in Gastric Cancer



14.2 Non-Small Cell Lung Cancer

Study 3 was a multinational, randomized, double-blind, study of CYRAMZA plus docetaxel versus placebo plus docetaxel, that randomized (1:1) 1253 patients with NSCLC with disease progression on or after one platinum-based therapy for locally advanced or metastatic disease. The major efficacy outcome measure was overall survival and the supportive efficacy outcome measures were progression-free survival and objective response rate. Patients were also required to have ECOG PS 0 or 1. Patients were randomized to receive either CYRAMZA at 10 mg/kg or placebo by intravenous infusion, in combination with docetaxel at 75 mg/m^2 every 21 days. Sites in East Asia administered a reduced dose of docetaxel at 60 mg/m^2 every 21 days. Patients who discontinued combination therapy because of an adverse event attributed to either CYRAMZA/placebo or docetaxel were permitted to continue monotherapy with the other treatment component until disease progression or intolerable toxicity. Randomization was stratified by geographic region, gender, prior maintenance therapy, and ECOG PS.

Demographics and baseline characteristics were similar between treatment arms. Median age was 62 years; 67% of patients were men; 82% were White and 13% were Asian; 32% had ECOG PS 0; 73% had nonsquamous histology and 26% had squamous histology. In addition to platinum chemotherapy (99%), the most common prior therapies were pemetrexed (38%), gemcitabine (25%), taxane (24%), and bevacizumab (14%). Twenty-two percent of patients received prior maintenance therapy. Tumor EGFR status was unknown for the majority of patients (65%). Where tumor EGFR status was known (n=445), 7.5% were positive for EGFR mutation (n=33). No data were collected regarding tumor ALK rearrangement status.

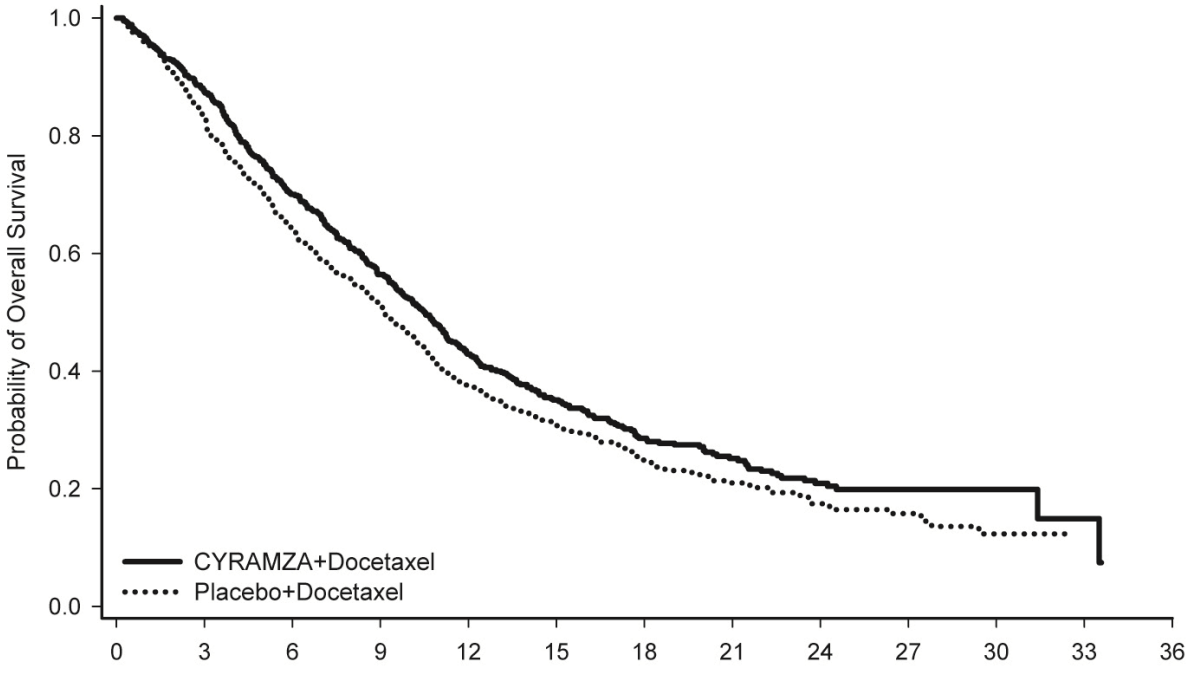
Overall survival and progression-free survival were statistically significantly improved in patients randomized to receive CYRAMZA plus docetaxel compared to patients randomized to receive placebo plus docetaxel. Objective response rate (complete response + partial response) was 23% (95% CI: 20, 26) for CYRAMZA plus docetaxel and 14% (95% CI: 11, 17) for placebo plus docetaxel, p-value of <0.001. Efficacy results are shown in Table 8 and Figure 3.

Table 8: Randomized Trial of CYRAMZA plus Docetaxel versus Placebo plus Docetaxel in NSCLC

	CYRAMZA + docetaxel N=628	**Placebo + docetaxel N=625**
Overall Survival		
Number of deaths (%)	428 (68%)	456 (73%)
Median – months (95% CI)	10.5 (9.5, 11.2)	9.1 (8.4, 10.0)
Hazard Ratio (95% CI)	0.86 (0.75, 0.98)	
Stratified Log-rank p-value	0.024	
Progression-free Survival		
Number of events (%)	558 (89%)	583 (93%)
Median – months (95% CI)	4.5 (4.2, 5.4)	3.0 (2.8, 3.9)
Hazard Ratio (95% CI)	0.76 (0.68, 0.86)	
Stratified Log-rank p-value	<0.001	

Abbreviations: CI = confidence interval

Figure 3: Kaplan-Meier Curves of Overall Survival - CYRAMZA plus Docetaxel versus Placebo plus Docetaxel in NSCLC



Number at Risk													
CYRAMZA+Docetaxel	628	527	415	329	231	156	103	70	45	23	11	2	0
Placebo+Docetaxel	625	501	386	306	197	129	86	56	36	23	9	0	0

14.3 Colorectal Cancer

Study 4 was a multinational, randomized, double-blind, study of CYRAMZA plus FOLFIRI versus placebo plus FOLFIRI, in patients with mCRC, who had disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Patients were required to have ECOG PS 0 or 1 and to have disease progression within 6 months of the last dose of first-line therapy. A total of 1072 patients were randomized (1:1) to receive either CYRAMZA (n=536) at 8 mg/kg as an intravenous infusion or placebo (n=536), in combination with FOLFIRI: irinotecan 180 mg/m^2 administered intravenously over 90 minutes and folinic acid 400 mg/m^2 administered intravenously simultaneously over 120 minutes; followed by 5-fluorouracil 400 mg/m^2 intravenous bolus over 2 to 4 minutes; followed by 5-fluorouracil 2400 mg/m^2 administered intravenously by continuous infusion over 46 to 48 hours. Treatment cycles on both arms were repeated every 2 weeks. Patients who discontinued one or more components of treatment because of an adverse event were permitted to continue therapy with the other treatment component(s) until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival and the supportive efficacy outcome measure was progression-free survival. Randomization was stratified by geographic region, tumor KRAS status, and time to disease progression after beginning first-line treatment (<6 months versus ≥6 months).

Demographic and baseline characteristics were similar between treatment arms. Median age was 62 years; 57% of patients were men; 76% were White and 20% Asian; 49% had ECOG PS 0; 49% of patients had KRAS mutant tumors; and 24% of patients had <6 months from time to disease progression after beginning first-line treatment.

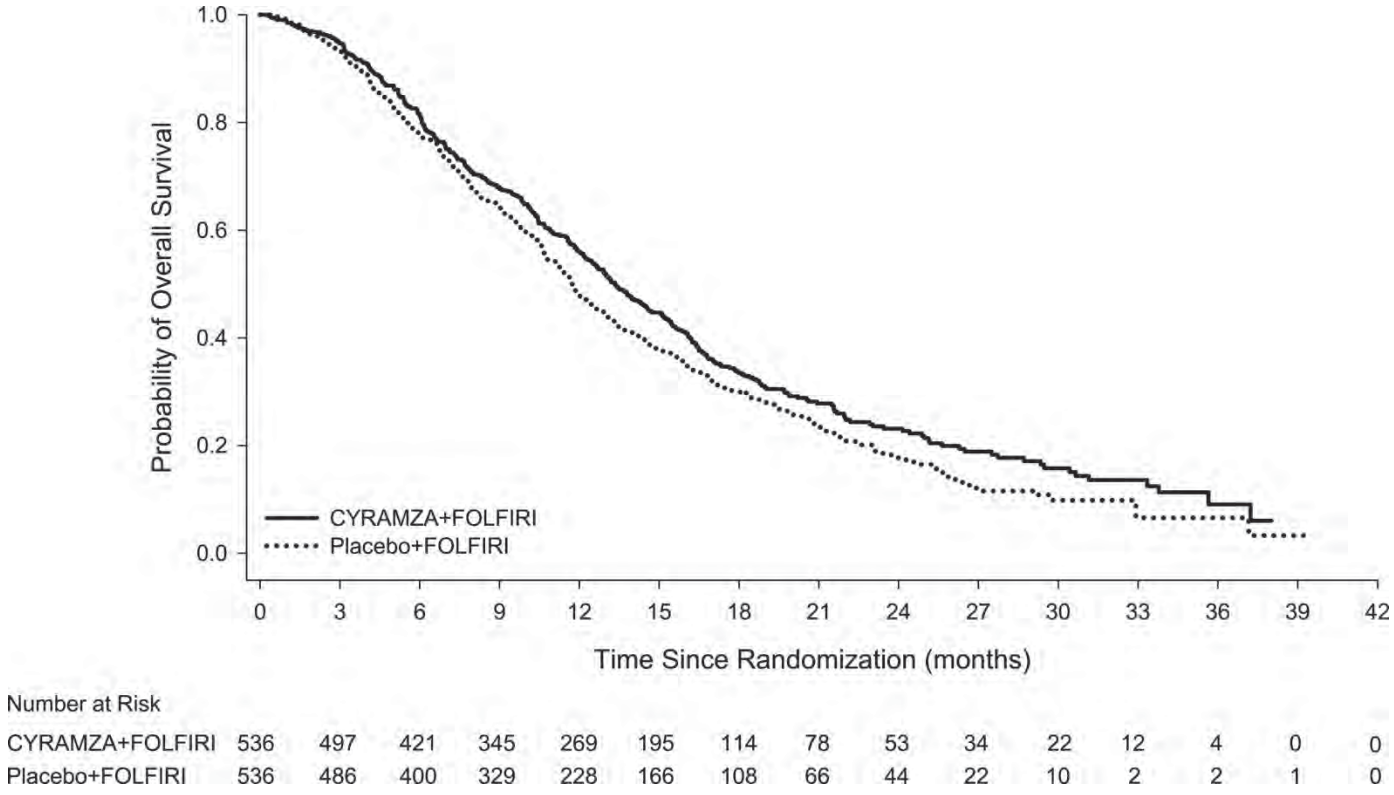
Overall survival and progression-free survival were statistically significantly improved in patients randomized to receive CYRAMZA plus FOLFIRI compared to patients randomized to receive placebo plus FOLFIRI. The treatment effect was consistent across the pre-specified stratification factors. Efficacy results are shown in Table 9 and Figure 4.

Table 9: Randomized Trial of CYRAMZA plus FOLFIRI versus Placebo plus FOLFIRI in mCRC

	CYRAMZA + FOLFIRI N=536	Placebo + FOLFIRI N=536
Overall Survival		
Number of deaths (%)	372 (69%)	397 (74%)
Median – months (95% CI)	13.3 (12.4, 14.5)	11.7 (10.8, 12.7)
Hazard Ratio (95% CI)	0.85 (0.73, 0.98)	
Stratified Log-rank p-value	0.023	
Progression-free Survival		
Number of events (%)	476 (89%)	494 (92%)
Median – months (95% CI)	5.7 (5.5, 6.2)	4.5 (4.2, 5.4)
Hazard Ratio (95% CI)	0.79 (0.70, 0.90)	
Stratified Log-rank p-value	<0.001	

Abbreviations: CI = confidence interval.

Figure 4: Kaplan-Meier Curve of Overall Survival - CYRAMZA plus FOLFIRI versus Placebo plus FOLFIRI in mCRC



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

CYRAMZA is supplied in single-dose vials as a sterile, preservative-free solution.

- NDC 0002-7669-01
  100 mg/10 mL (10 mg/mL), individually packaged in a carton
- NDC 0002-7678-01
  500 mg/50 mL (10 mg/mL), individually packaged in a carton

16.2 Storage and Handling

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light. **DO NOT FREEZE OR SHAKE** the vial.

17 PATIENT COUNSELING INFORMATION

- **Hemorrhage:**
  Advise patients that CYRAMZA can cause severe bleeding. Advise patients to contact their health care provider for bleeding or symptoms of bleeding including lightheadedness *[see Warnings and Precautions (5.1)]*.
- **Arterial thromboembolic events:**
  Advise patients of an increased risk of an arterial thromboembolic event *[see Warnings and Precautions (5.2)]*.
- **Hypertension:**
  Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms *[see Warnings and Precautions (5.3)]*.
- **Gastrointestinal perforations:**
  Advise patients to notify their health care provider for severe diarrhea, vomiting, or severe abdominal pain *[see Warnings and Precautions (5.5)]*.
- **Impaired wound healing:**
  Advise patients that CYRAMZA has the potential to impair wound healing. Instruct patients not to undergo surgery without first discussing this potential risk with their health care provider *[see Warnings and Precautions (5.6)]*.
- **Pregnancy and fetal harm:**
  Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and infant development and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1, 8.3)]*.
- **Lactation:**
  Advise patients not to breastfeed during CYRAMZA treatment *[see Use in Specific Populations (8.2)]*.
- **Infertility:**
  Advise females of reproductive potential regarding potential infertility effects of CYRAMZA *[see Use in Specific Populations (8.3)]*.

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Eli Lilly and Company, Indianapolis, IN 46285, USA

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