

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 infusion
Initial U.S. Approval: 2014

WARNING: HEMORRHAGE

See full prescribing information for complete boxed warning.

CYRAMZA increased the risk of 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)].

RECENT MAJOR CHANGES

Indications and Usage	11/2014
Dosage and Administration:	
Recommended Dose and Schedule (2.1)	11/2014
Warnings and Precautions:	
Hemorrhage (5.1)	11/2014
Hypertension (5.3)	11/2014
Gastrointestinal Perforations (5.5)	11/2014

INDICATIONS AND USAGE

CYRAMZA® is a human vascular endothelial growth factor receptor 2 antagonist indicated for the treatment of:

Gastric Cancer

- Advanced gastric or gastro-esophageal junction adenocarcinoma, as a single agent or in combination with paclitaxel, after prior fluoropyrimidine- or platinum-containing chemotherapy. (1)

DOSAGE AND ADMINISTRATION

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

- 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, 2.5)

DOSAGE FORMS AND STRENGTHS

- 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

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)
- Gastrointestinal Perforation: Discontinue CYRAMZA. (5.5)
- 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)

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)

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

- Pregnancy: Based on its mechanism of action, CYRAMZA may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue nursing or discontinue CYRAMZA. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2014

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FULL PRESCRIBING INFORMATION**WARNING: HEMORRHAGE**

CYRAMZA increased the risk of 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)].

1 INDICATIONS AND USAGE**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.

2 DOSAGE AND ADMINISTRATION

Do not administer CYRAMZA as an intravenous push or bolus.

2.1 Recommended Dose and Schedule

- 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.

2.2 Premedication

- Prior to each CYRAMZA infusion, premedicate all patients with an intravenous histamine H₁ antagonist (e.g., diphenhydramine hydrochloride).
- For patients who have experienced a Grade 1 or 2 infusion reaction, also premedicate with dexamethasone (or equivalent) and acetaminophen prior to each CYRAMZA infusion [see Dosage and Administration (2.3)].

2.3 Dose ModificationsInfusion-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 of 6 mg/kg every 2 weeks 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 to 5 mg/kg every 2 weeks 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 Adverse Reactions (6.1)].

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, 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

- 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 non steroid anti-inflammatory drugs (NSAIDs) were excluded from enrollment in Studies 1 and 2; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding [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%) and in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%).

Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 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, infusion-related reactions (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 perforations was also increased in patients that received CYRAMZA plus paclitaxel (1.2%) as compared to patients receiving placebo plus paclitaxel (0.3%).

Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation [see *Dosage and Administration* (2.3)].

5.6 Impaired Wound Healing

CYRAMZA has not been studied in patients with serious or non-healing wounds. CYRAMZA is an antiangiogenic therapy with the potential to adversely affect 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 (RPLS)

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.

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)].

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.

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/m² 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 ECOG performance status 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 $\geq 10\%$ and $\geq 2\%$ 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 1 provides the frequency and severity of adverse reactions in Study 1.

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

Adverse Reactions (MedDRA) ^a 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

^a MedDRA Version 15.0.

Clinically relevant adverse reactions reported in $\geq 1\%$ 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 60 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 $\geq 30\%$ and $\geq 2\%$ 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 2 provides the frequency and severity of adverse reactions in Study 2.

Table 2: Adverse Reactions Occurring at Incidence Rate $\geq 5\%$ and a $\geq 2\%$ 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 $\geq 1\%$ 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).

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials, 53/884 (6%) of CYRAMZA-treated patients with post baseline serum samples tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). However, this assay has limitations in detecting anti-ramucirumab antibodies in the presence of ramucirumab; therefore, the incidence of antibody development may not have been reliably determined. Neutralizing antibodies were detected in 9 of the 53 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 (PK) interactions were observed between ramucirumab and paclitaxel [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

Based on its mechanism of action, CYRAMZA may 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 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.

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 fetoplacental 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.

8.3 Nursing Mothers

It is not known whether CYRAMZA is excreted in human milk. No studies have been conducted to assess CYRAMZA's impact on milk production or its presence in breast milk. Human IgG is excreted in human milk, but published data suggests that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are excreted in human milk and because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

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, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. [see *Clinical Studies (14)*]

8.6 Renal Impairment

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

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin >1.0-1.5 times upper limit of normal [ULN] and any AST) based on population PK 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)*].

8.8 Females and Males of Reproductive Potential

Fertility

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

Contraception

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

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

With the dosing regimen of 8 mg/kg every 2 weeks in patients with advanced gastric or gastro-esophageal junction cancer, the geometric means of the minimum ramucirumab concentrations (C_{min}) were 50 $\mu\text{g/mL}$ (6-228 $\mu\text{g/mL}$) after the third dose and 74 $\mu\text{g/mL}$ (14-234 $\mu\text{g/mL}$) after the sixth dose. Similar C_{min} values of ramucirumab were observed when ramucirumab was administered with paclitaxel.

Based on a population PK analysis, the mean (% coefficient of variation [CV%]) volume of distribution at steady state for ramucirumab was 5.5 L (14%), the mean clearance was 0.014 L/hour (30%), and the mean elimination half-life was 15 days (24%).

Specific Populations

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

Renal Impairment: The effect of renal impairment on the average concentration of ramucirumab at steady state (C_{ss}) was evaluated in patients with mild (calculated creatinine clearance [CLcr] 60-89 mL/min, n=204), moderate (CLcr 30-59 mL/min, n=91) or severe (CLcr 15 -29 mL/min, n=3) renal impairment compared to patients with normal renal function (CLcr \geq 90 mL/min, n=198) in a population PK analysis. No clinically meaningful differences in the average C_{ss} of ramucirumab were observed between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the average C_{ss} of ramucirumab was evaluated in patients with mild (total bilirubin >1.0-1.5 times upper limit of normal [ULN] and any AST, n=107) or moderate hepatic impairment (total bilirubin >1.5-3.0 times ULN and any AST, n=3) compared to patients with normal hepatic function (total bilirubin and AST \leq ULN, n=386) in a population PK analysis. No clinically meaningful differences in the average C_{ss} of ramucirumab were found between patients with mild or moderate hepatic impairment and patients with normal hepatic function. No PK data were available from patients with severe hepatic dysfunction (total bilirubin >3.0 times ULN and any AST).

Drug Interaction Studies

No clinically meaningful changes in paclitaxel exposure or ramucirumab exposure were observed when CYRAMZA 8 mg/kg and paclitaxel 80 mg/m² were co-administered 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 with 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

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 Eastern Cooperative Oncology Group (ECOG) performance status (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 ($\geq 10\%$ 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.

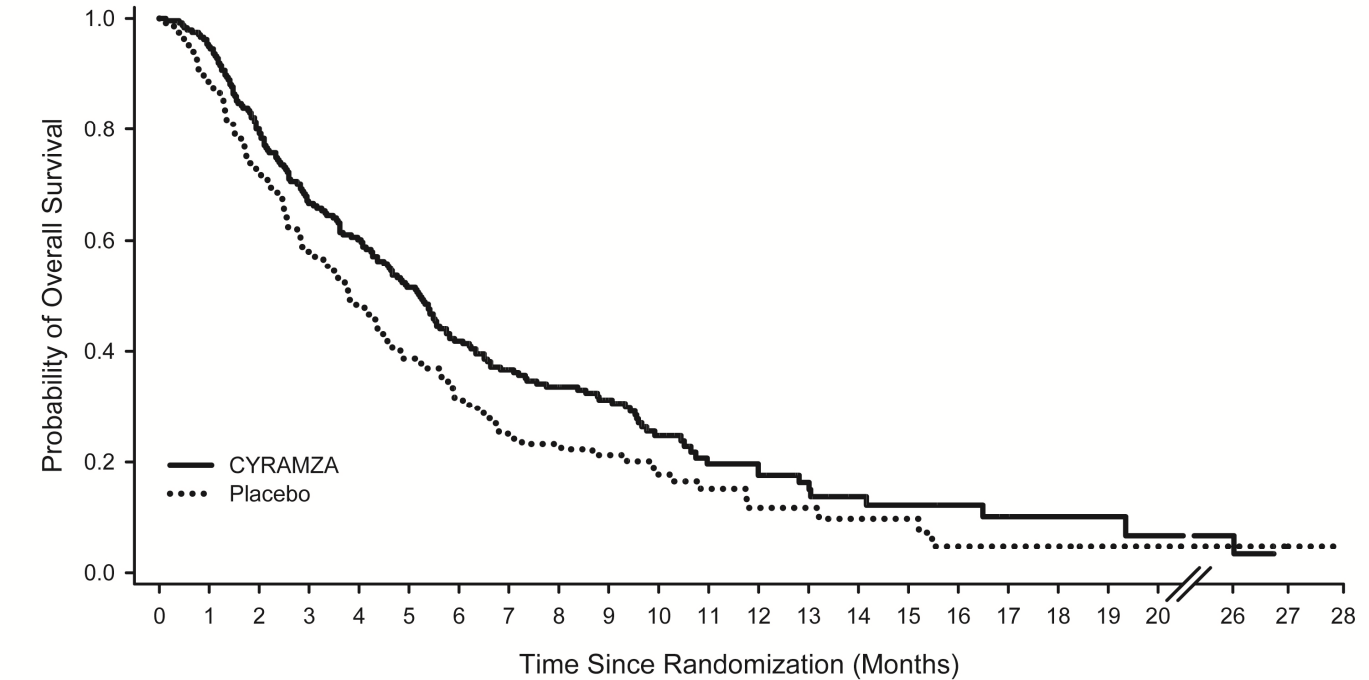
Overall survival and progression-free survival were statistically significantly improved in patients randomized to receive CYRAMZA as compared to patients randomized to receive placebo. Efficacy results are shown in Table 3 and Figure 1.

Table 3: Efficacy Results

	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 in Study 1



	Number at Risk									
CYRAMZA	238	154	92	49	17	7	3		0	0
Placebo	117	66	34	20	7	4	2		1	0

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 \geq 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/m² 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/m² 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.

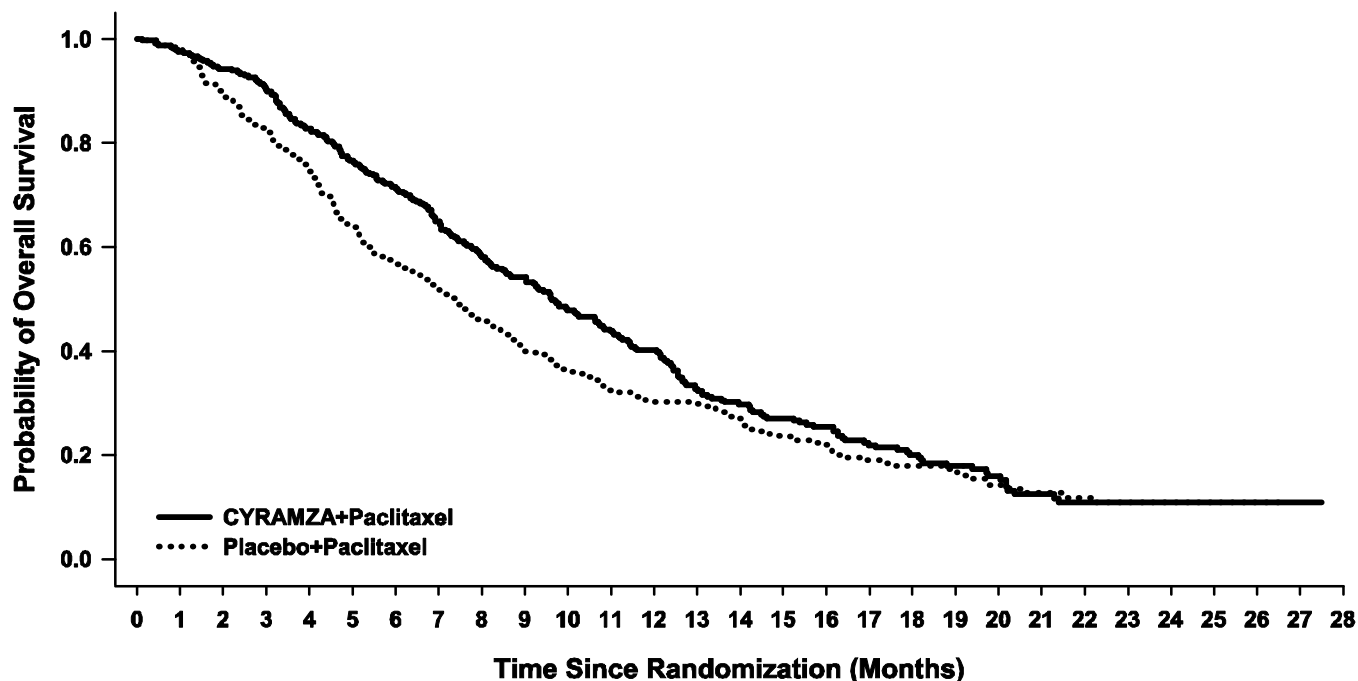
Overall survival, progression-free survival, and objective response rate were statistically significantly improved in patients randomized to receive CYRAMZA plus paclitaxel compared to patients randomized to receive placebo plus paclitaxel. Efficacy results are shown in Table 4 and Figure 2.

Table 4: Summary of Efficacy Data – Intent to Treat (ITT) Population

	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 in Study 2



Number at Risk

CYRAMZA+Paclitaxel	330	308	267	228	185	148	116	78	60	41	24	13	6	1	0
Placebo+Paclitaxel	335	294	241	180	143	109	81	64	47	30	22	13	5	2	0

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.

For product diluted in 0.9% sodium chloride, the chemical and physical stability have been demonstrated for up to 24 hours at 2°C to 8°C (36°F to 46°F) or for 4 hours at room temperature (below 25°C [77°F]). **DO NOT FREEZE OR SHAKE** the diluted product.

17 PATIENT COUNSELING INFORMATION

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)].
- Of increased risk of an arterial thromboembolic event [see *Warnings and Precautions* (5.2)].
- 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)].
- To notify their health care provider for severe diarrhea, vomiting, or severe abdominal pain [see *Warnings and Precautions* (5.5)].
- 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)].
- Of the potential risk for maintaining pregnancy, risk to the fetus, or risk to postnatal development during and following treatment with CYRAMZA and the need to avoid getting pregnant, including use of adequate contraception, for at least 3 months following the last dose of CYRAMZA [see *Use in Specific Populations* (8.1, 8.8)].
- To discontinue nursing during CYRAMZA treatment [see *Use in Specific Populations* (8.3)].

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