Billing and Coding Guide

INDICATIONS

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

- CYRAMZA, in combination with erlotinib, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

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

- CYRAMZA, in combination with FOLFIRI (irinotecan, folinic acid, and 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.

- CYRAMZA, as a single agent, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have an alpha-fetoprotein (AFP) of ≥400 ng/mL and have been treated with sorafenib.

SELECT IMPORTANT SAFETY INFORMATION

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%.

- Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown.

- Patients with NSCLC receiving therapeutic anticoagulation or with evidence of major airway invasion by cancer were excluded from REVEL. In addition, patients with NSCLC with a recent history of gross hemoptysis, those receiving 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 REVEL and RELAY; therefore the risk of pulmonary hemorrhage in these groups of patients is unknown.

- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

The following information is presented for informational purposes only and is not intended to provide reimbursement or legal advice. Laws, regulations, and policies concerning reimbursement are complex and are updated frequently. Individual coding decisions should be based upon diagnosis and treatment of individual patients. While we have made an effort to be current as of the issue date of this document, the information may not be as current or comprehensive when you view it. Providers are encouraged to contact third-party payers for specific information on their coverage, coding, and payment policies. Please consult with your legal counsel or reimbursement specialist for any reimbursement or billing questions. For more information please call the Lilly Oncology Support Center at 1-866-472-8663.

Please see Important Safety Information on pages 16-19 and full Prescribing Information for CYRAMZA.
The CYRAMZA Billing and Coding Guide is an all-indication reimbursement support resource.

Within this resource you will find:
- Dosing and administration information
- Diagnosis codes
- Healthcare Common Procedure Coding System (HCPCS) codes
- National Drug Codes (NDC)
- Sample claim forms for outpatient hospital facilities and physicians’ offices
- Lilly Oncology Support Center information for patients who may need additional assistance

SELECT IMPORTANT SAFETY INFORMATION

Gastrointestinal Perforations
- CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%.
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.
Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer CYRAMZA Billing and Coding Information

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

**CYRAMZA Dosing**
- The recommended dose of CYRAMZA, either as a single agent or in combination with weekly paclitaxel, is 8 mg/kg every 2 weeks administered by intravenous (IV) infusion over 60 minutes
- If the first infusion is tolerated, all subsequent CYRAMZA infusions may be administered over 30 minutes
- Do not administer CYRAMZA as an IV push or bolus
- Continue CYRAMZA until disease progression or unacceptable toxicity
- When given in combination with paclitaxel, administer CYRAMZA prior to administration of paclitaxel
- Refer to the Prescribing Information for paclitaxel for dosage information

**SELECT IMPORTANT SAFETY INFORMATION**

**Infusion-Related Reactions (IRR)**
- IRR, including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. Symptoms of IRR 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. In 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from <1-9%. Grade 3-5 IRR incidence was <1%.
- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

**Diagnosis Code for Gastroesophageal Junction Cancer**
Use this diagnosis code specifically for GEJ cancer.

<table>
<thead>
<tr>
<th>ICD-10 Code*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C16.0</td>
<td>Cardia, cardiac orifice, cardio-esophageal junction, gastroesophageal junction, esophagus, and stomach</td>
</tr>
</tbody>
</table>

**Diagnosis Codes for Gastric Cancer**

<table>
<thead>
<tr>
<th>ICD-10 Code*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C16.0</td>
<td>Cardia</td>
</tr>
<tr>
<td>C16.1</td>
<td>Fundus of stomach</td>
</tr>
<tr>
<td>C16.2</td>
<td>Body of stomach</td>
</tr>
<tr>
<td>C16.3</td>
<td>Pyloric antrum</td>
</tr>
<tr>
<td>C16.4</td>
<td>Pylorus</td>
</tr>
<tr>
<td>C16.5</td>
<td>Lesser curvature of stomach, unspecified</td>
</tr>
<tr>
<td>C16.6</td>
<td>Greater curvature of stomach, unspecified</td>
</tr>
<tr>
<td>C16.8</td>
<td>Overlapping sites of stomach</td>
</tr>
<tr>
<td>C16.9</td>
<td>Stomach, unspecified site</td>
</tr>
</tbody>
</table>

**Click here to see Premedication and Dose Modifications for CYRAMZA on page 15.**

**HCPCS Code**

<table>
<thead>
<tr>
<th>CYRAMZA Specific Code</th>
<th>Description</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>J9308</td>
<td>Injection, ramucirumab, 5 mg</td>
<td>Physician office and hospital outpatient</td>
</tr>
</tbody>
</table>

**NDC**
CYRAMZA is available in 100 mg/10 mL and 500 mg/50 mL (10 mg/mL) solution, single-dose vials.

**Drug Administration CPT Code**

<table>
<thead>
<tr>
<th>Vial Size</th>
<th>NDC†</th>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg/10 mL</td>
<td>00002-7669-01</td>
<td>96413</td>
<td>Chemotherapy administration, intravenous infusion technique, up to 1 hour, single or initial substance/drug</td>
</tr>
<tr>
<td>500 mg/50 mL</td>
<td>00002-7678-01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Please check to ensure that codes are used to the highest level of specificity. Providers should use current ICD-10-CM codes to report a patient’s diagnosis on claim submissions. This list of ICD-10-CM diagnosis codes may be reasonably related to a diagnosis within the product’s approved label. Other codes may be appropriate.

†FDA standard NDC has been “zero-filled” to ensure creation of an 11-digit code that meets HIPAA standards. The zero-fill location is indicated in bold.


CPT is a registered trademark of the American Medical Association.
† Please note that this is not an all-inclusive list of available diagnostic tests and testing methods to identify EGFR gene alterations. The laboratory is responsible for selecting the appropriate billing code for the test that is performed.

CPT codes for EGFR mutation testing modalities that may be used†

<table>
<thead>
<tr>
<th>Test Method</th>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Next Generation Sequencing (NGS)</td>
<td>81145</td>
<td>Targeted genomic sequence analysis panel, solid organ neoplasm, DNA and RNA analysis, 5-50 genes</td>
</tr>
<tr>
<td></td>
<td>81155</td>
<td>Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA and RNA analysis, ≤ 50 genes</td>
</tr>
<tr>
<td></td>
<td>0022U</td>
<td>Oncomine DX Target Test; Targeted genomic sequence analysis panel, NSCLC, DNA and RNA analysis of 23 genes</td>
</tr>
<tr>
<td></td>
<td>0037U</td>
<td>FoundationOne CDx, Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes</td>
</tr>
<tr>
<td></td>
<td>0048U</td>
<td>MSK-IMPACT, Oncology (solid organ neoplasm), DNA, targeted sequencing of protein-coding exons of 468 genes</td>
</tr>
<tr>
<td>Acromegalic Pathology</td>
<td>88356</td>
<td>In situ hybridization (ISH), FISH, per specimen; initial single probe stain procedure</td>
</tr>
<tr>
<td></td>
<td>88376</td>
<td>Morphometric analysis, each multiplex probe stain procedure; automated</td>
</tr>
<tr>
<td></td>
<td>88377</td>
<td>Morphometric analysis, each multiplex probe stain procedure; manual</td>
</tr>
<tr>
<td></td>
<td>88342</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain</td>
</tr>
</tbody>
</table>

Notes: Per AMA CPT Code Book 2019, applicable CPT codes for EGFR as denoted by the Molecular Pathology Gene Table include 81235, 81445, and 81455. CPT is a registered trademark of the American Medical Association.

*Refer to the Prescribing Information for erlotinib for dosing information.

 § Please check to ensure that codes are used to the highest level of specificity. Providers should use current ICD-10-MMS codes to report a patient’s diagnosis on claim submissions. This list of ICD-10-MMS diagnosis codes may be reasonably related to a diagnosis within the product’s approved label. Other codes may be appropriate.

¶ FDA standard NDC has been “zero-filled” to ensure creation of an 11-digit code that meets HIPAA standards. The zero-fill location is indicated in bold.

CYPARMA First-line Dosing (In Combination With Erlotinib)

• The recommended dosage of CYRAMZA is 10 mg/kg every 2 weeks administered by IV infusion over 60 minutes

• In the event of a Grade 1 or 2 IRR, reduce infusion rate by 50%

• Erlotinib 150 mg per day orally*

CYRAMZA Second-line Dosing (In Combination With Docetaxel)

• The recommended dosage of CYRAMZA is 10 mg/kg administered by IV infusion over 60 minutes on Day 1 of a 21-day cycle prior to docetaxel infusion

• For IV infusion only. Do not administer as IV push or bolus

• Refer to the Prescribing Information for docetaxel for dosage information

CYRAMZA General Dosing - Additional Information

• If the first infusion is tolerated, all subsequent CYRAMZA infusions may be administered over 30 minutes

• Continue CYRAMZA until disease progression or unacceptable toxicity

Click here to see Premedication and Dose Modifications for CYRAMZA on page 15.

All coding and documentation requirements for drugs should be confirmed with each payer.

Diagnosis Codes for NSCLC

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C33</td>
<td>Trachea</td>
</tr>
<tr>
<td>C34.00</td>
<td>Unspecified main bronchus</td>
</tr>
<tr>
<td>C34.01</td>
<td>Right main bronchus</td>
</tr>
<tr>
<td>C34.02</td>
<td>Left main bronchus</td>
</tr>
<tr>
<td>C34.10</td>
<td>Upper lobe, unspecified bronchus or lung</td>
</tr>
<tr>
<td>C34.11</td>
<td>Upper lobe, right bronchus or lung</td>
</tr>
<tr>
<td>C34.12</td>
<td>Upper lobe, left bronchus or lung</td>
</tr>
<tr>
<td>C34.20</td>
<td>Middle lobe, bronchus or lung</td>
</tr>
<tr>
<td>C34.30</td>
<td>Lower lobe, unspecified bronchus or lung</td>
</tr>
<tr>
<td>C34.31</td>
<td>Lower lobe, right bronchus or lung</td>
</tr>
<tr>
<td>C34.32</td>
<td>Lower lobe, left bronchus or lung</td>
</tr>
<tr>
<td>C34.80</td>
<td>Overlapping sites of unspecified bronchus and lung</td>
</tr>
<tr>
<td>C34.81</td>
<td>Overlapping sites of right bronchus and lung</td>
</tr>
<tr>
<td>C34.82</td>
<td>Overlapping sites of left bronchus and lung</td>
</tr>
<tr>
<td>C34.90</td>
<td>Unspecified part of unspecified bronchus or lung</td>
</tr>
<tr>
<td>C34.91</td>
<td>Unspecified part of right bronchus or lung</td>
</tr>
<tr>
<td>C34.92</td>
<td>Unspecified part of left bronchus or lung</td>
</tr>
</tbody>
</table>

Notes: Per AMA CPT Code Book 2019, applicable CPT codes for EGFR as denoted by the Molecular Pathology Gene Table include 81235, 81445, and 81455. CPT is a registered trademark of the American Medical Association.

*Refer to the Prescribing Information for erlotinib for dosing information.

Please see Important Safety Information on pages 16-19 and full Prescribing Information for CYRAMZA.

HPCPCS Code

<table>
<thead>
<tr>
<th>CYRAMZA Specific Code</th>
<th>Description</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1368</td>
<td>Injection, ramucirumab, 5 mg</td>
<td>Physician office and hospital outpatient</td>
</tr>
</tbody>
</table>

NDC

<table>
<thead>
<tr>
<th>Vial Size</th>
<th>NDC*</th>
<th>CPT Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg/10 mL</td>
<td>00002-7649-01</td>
<td>96413</td>
</tr>
<tr>
<td>500 mg/50 mL</td>
<td>00002-7678-01</td>
<td></td>
</tr>
</tbody>
</table>

*Please check to ensure that codes are used to the highest level of specificity. Providers should use current ICD-10-MMS codes to report a patient’s diagnosis on claim submissions. This list of ICD-10-MMS diagnosis codes may be reasonably related to a diagnosis within the product’s approved label. Other codes may be appropriate.

FDA standard NDC has been “zero-filled” to ensure creation of an 11-digit code that meets HIPAA standards. The zero-fill location is indicated in bold.


SELECT IMPORTANT SAFETY INFORMATION

Infusion-Related Reactions (IRR)

• IRR, including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. Symptoms of IRR included rashes/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasms, supraventricular tachycardia, and hypotension. In 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from 1-19%. Grade 3-5 IRR incidence was <1%.

• Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

Please see Important Safety Information on pages 16-19 and full Prescribing Information for CYRAMZA.
Metastatic Colorectal Cancer

CYRAMZA Billing and Coding Information

Indication

CYRAMZA in combination with FOLFIRI (irinotecan, folinic acid, and 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.

CYRAMZA Dosing

- The recommended dosage of CYRAMZA is 8 mg/kg every 2 weeks administered by IV infusion over 60 minutes prior to FOLFIRI administration
- If the first infusion is tolerated, all subsequent CYRAMZA infusions may be administered over 30 minutes
- Do not administer as an IV push or bolus
- Continue CYRAMZA until disease progression or unacceptable toxicity
- Refer to the Prescribing Information for fluorouracil, leucovorin, and irinotecan for dosing information

AFP-High (≥400 ng/mL) Hepatocellular Carcinoma

CYRAMZA Billing and Coding Information

Indication

CYRAMZA, as a single agent, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have an alpha-fetoprotein (AFP) of ≥400 ng/mL and have been treated with sorafenib.

CYRAMZA Dosing

- Do not administer as IV push or bolus
- The recommended dosage of CYRAMZA is 8 mg/kg every 2 weeks administered by IV infusion over 60 minutes. If the first infusion is tolerated, all subsequent CYRAMZA infusions may be administered over 30 minutes
- Continue CYRAMZA until disease progression or unacceptable toxicity

Diagnosis Codes for HCC

ICD-10 Code† Description
C22.0 Liver cell carcinoma
C22.8 Malignant neoplasm of liver, primary, unspecified as to type

HCPCS Codes for CRC and HCC

CYRAMZA Specific Code Description Setting
J9308 Injection, ramucirumab, 5 mg Physician office and hospital outpatient

NDC for CRC and HCC

CYRAMZA is available in 100 mg/10 mL and 500 mg/50 mL (10 mg/mL) solution, single-dose vials.

Drug Administration CPT Code for CRC and HCC

NDC: 100 mg/10 mL, 500 mg/50 mL CPT Code Description
0002-7669-01 96413 Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
0002-7678-01

Infusion-Related Reactions (IRR)

- IRR, including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. Symptoms of IRR included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and pareshisia.
- In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. In 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from <1-9%. Grade 3-5 IRR incidence was <1%.
- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

Please see Important Safety Information on pages 16-19 and full Prescribing Information for CYRAMZA.
Sample Claim Form CMS-1450 (UB-04) (Hospital Outpatient)

FL 42 & 43: Revenue Codes and Description
Enter the revenue codes that correspond to HCPCS or CPT codes outlined in FL 44. Payers may vary on revenue code requirements for each procedure/service performed.

FL 44: Product and Procedure Coding
Enter the HCPCS drug code and CPT code for the administration of CYRAMZA.
HCPCS:
J9308: Injection, ramucirumab, 5 mg
CPT:
96413: Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug

FL 46: Service Units
One (1) billable unit=5 mg. Total units reported will depend on total dosage given. Please confirm specific billing requirements, including wastage, with each individual payer.

FL 66: Diagnosis Codes
Enter the appropriate ICD diagnosis code(s) that correspond(s) to the type and location of the disease with which the patient has been diagnosed.

FL 68: Remarks
To support the review and payment of the claim, include additional information as required by respective payers. This may include NDC, total dosage, and date CYRAMZA was administered.

All coding and documentation requirements for drugs should be confirmed with each payer.
Sample Claim Form CMS-1500
(Physician Office)

**BOX 19: Additional Claim Information**
Box 19 of the CMS-1500 claim form (or its electronic equivalent) is frequently utilized to obtain information regarding the use of drugs. The information will vary, but may include some or all of these items:
- Drug name
- NDC
- Date of treatment
- Total dose administered
- Route of administration
- Amount of drug wasted

Please refer to the payer’s most current instructions regarding the use of this field.

**BOX 21: Diagnosis of Illness or Injury**
Enter the appropriate diagnosis code in lines A-L to identify the patient’s diagnosis/condition and the applicable ICD indicator to identify which ICD code version is being reported. Use the highest level of specificity.

**BOX 24A: Date(s) of Service**
When required by payers to provide the NDC, enter the code.

**BOX 24D: Procedures, Services, or Supplies**
Enter the HCPCS or CPT code and modifier(s) from the appropriate code set.

- **HCPCS:**
  - J9308: Injection, ramucirumab, 5 mg

- **CPT:**
  - 96413: Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug

**BOX 24E: Diagnosis Pointer**
Enter the diagnosis code reference letter, as shown in Box 21, to relate the date of service and the procedures performed to the primary diagnosis. Enter only one reference letter per line item.

**BOX 24G: Days or Units**
One (1) billable unit=5 mg. Total units reported will depend on total dosage given. Please confirm specific billing requirements, including wastage, with each individual payer.

All coding and documentation requirements for drugs should be confirmed with each payer.
Lilly Oncology Support Center: Support and Reimbursement

Find resources and programs to help support your eligible patients during treatment

The Lilly Oncology Support Center is committed to helping qualified patients when they’re prescribed a Lilly Oncology product. We focus on financial and coverage issues, offering resources and individualized support for eligible patients, whether they’re uninsured, underinsured, or insured. Services include help with benefit verification, prior authorization, paying for medicine, and specialty-pharmacy coordination.

The Lilly Oncology Support Center also can provide support beyond financial assistance for certain products, and it helps patients connect with non-Lilly resources, such as therapeutic-support groups for specific types of cancer.

Savings Card Program
- Supports eligible, commercially insured patients with Savings Cards and coinsurance costs for prescribed Lilly Oncology products† for an FDA-approved use
- No income eligibility requirement

*The offer is invalid for patients whose prescription claims are eligible to be reimbursed, in whole or in part, by any governmental program.

For more information, visit LillyOncologySupportCenter.com.

Insurance Support
- Eligibility information
- Benefits investigation
- Prior authorization assistance
- Appeals information
- Specialty pharmacy coordination
- Billing and Coding information
- Payment methodologies and allowances
- Payer policy information

Resources

Dose Modifications for CYRAMZA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td></td>
<td>• Permanently discontinue CYRAMZA</td>
</tr>
<tr>
<td>Gastrointestinal Perforation</td>
<td>All Grades</td>
</tr>
<tr>
<td></td>
<td>• Permanently discontinue CYRAMZA</td>
</tr>
<tr>
<td>Wound Healing Complications</td>
<td>All Grades</td>
</tr>
<tr>
<td></td>
<td>• Withhold CYRAMZA for 28 days prior to elective surgery. Resume CYRAMZA no sooner than 2 weeks after surgery and until adequate wound healing has occurred.</td>
</tr>
<tr>
<td>Arterial/Thromboembolic Events</td>
<td>All Grades</td>
</tr>
<tr>
<td></td>
<td>• Permanently discontinue CYRAMZA</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Severe hypertension</td>
</tr>
<tr>
<td></td>
<td>• Withhold CYRAMZA until controlled with medical management</td>
</tr>
<tr>
<td>Infusion-Related Reaction (IRR)</td>
<td>Grade 1 or 2 IRR</td>
</tr>
<tr>
<td></td>
<td>• Reduce the infusion rate of CYRAMZA by 50%</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 IRR</td>
</tr>
<tr>
<td></td>
<td>• Permanently discontinue CYRAMZA</td>
</tr>
<tr>
<td>Posterior Reversible Encephalopathy Syndrome (PRES)</td>
<td>All Grades</td>
</tr>
<tr>
<td></td>
<td>• Permanently discontinue CYRAMZA</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>First occurrence of increased urine protein levels greater than or equal to 2 g per 24 hours</td>
</tr>
<tr>
<td></td>
<td>• Withhold CYRAMZA until urine protein level is less than 2 g per 24 hours</td>
</tr>
<tr>
<td></td>
<td>• Resume CYRAMZA at a reduced dose:</td>
</tr>
<tr>
<td></td>
<td>  Reduce 10 mg dose to 8 mg</td>
</tr>
<tr>
<td></td>
<td>  Reduce 8 mg dose to 6 mg</td>
</tr>
<tr>
<td></td>
<td>• Resume CYRAMZA at a reduced dose:</td>
</tr>
<tr>
<td></td>
<td>  Reduce 4 mg dose to 2 mg</td>
</tr>
<tr>
<td></td>
<td>• Resume CYRAMZA at a reduced dose:</td>
</tr>
<tr>
<td></td>
<td>  Reduce 2 mg dose to 1 mg</td>
</tr>
<tr>
<td>Uremia</td>
<td>Proteinuria and/or a decrease in estimated glomerular filtration rate (GFR) (eg, renal failure)</td>
</tr>
<tr>
<td></td>
<td>• Permanently discontinue CYRAMZA</td>
</tr>
</tbody>
</table>

Dose Modification for CYRAMZA

- Prior to each CYRAMZA infusion, premedicate all patients with an IV histamine-1 receptor antagonist (eg, diphenhydramine hydrochloride)
- For patients who have experienced a grade 1 or 2 IRR, premedicate with a histamine-1 receptor antagonist, dexamethasone (or equivalent), and acetaminophen prior to each CYRAMZA infusion

Premedication and Dose Modification Information for All CYRAMZA Indications

Premedication for CYRAMZA
- Prior to each CYRAMZA infusion, premedicate all patients with an IV histamine-1 receptor antagonist (eg, diphenhydramine hydrochloride)
- For patients who have experienced a grade 1 or 2 IRR, premedicate with a histamine-1 receptor antagonist, dexamethasone (or equivalent), and acetaminophen prior to each CYRAMZA infusion

Dose Modifications for CYRAMZA

- Prior to each CYRAMZA infusion, premedicate all patients with an IV histamine-1 receptor antagonist (eg, diphenhydramine hydrochloride)
- For patients who have experienced a grade 1 or 2 IRR, premedicate with a histamine-1 receptor antagonist, dexamethasone (or equivalent), and acetaminophen prior to each CYRAMZA infusion

Please see Important Safety Information on pages 16-19 and full Prescribing Information for CYRAMZA.

SELECT IMPORTANT SAFETY INFORMATION

Infusion-Related Reactions (IRR)
- IRR, including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. Symptoms of IRR included rashes, 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. In 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all GRADE IRR ranged from <1-9%. Grade 3-5 IRR incidence was <1%
- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

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- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.
Important Safety Information for CYRAMZA® (ramucirumab)

**Hemorrhage** - CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%.

- Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW, therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown.

- Patients with NSCLC receiving therapeutic anticoagulation or with evidence of major airway invasion by cancer were excluded from REVEL. In addition, patients with NSCLC with a recent history of gross hemoptysis, those receiving chronic therapy with NSAIDs or other anti-platelet therapy other than once daily aspirin or with radiographic evidence of major blood vessel invasion or intratumor cavitation were excluded from REVEL and RELAY; therefore the risk of pulmonary hemorrhage in these groups of patients is unknown.

- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

**Gastrointestinal Perforations** - CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%.

- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

**Impaired Wound Healing** - CYRAMZA has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.

- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 2 weeks following a major surgical procedure and until adequate wound healing. The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.

**Arterial Thromboembolic Events (ATEs)** - Serious, sometimes fatal, ATEs, including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 1-3%. Grade 3-5 ATE incidence was <1-2%.

- Permanently discontinue CYRAMZA in patients who experience an ATE.

**Hypertension** - An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. Across five clinical trials, excluding NSCLC, in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension ranged from 11-26%. Grade 3-5 hypertension incidence ranged from 6-15%. In 221 patients with NSCLC receiving CYRAMZA in combination with erlotinib in the RELAY study, the incidence of new or worsening hypertension was higher (45%), as was the incidence of Grade 3-5 hypertension (24%). Of the patients experiencing new or worsening hypertension in RELAY (N=100 CYRAMZA and erlotinib; N=27 placebo and erlotinib), 13% of those treated with CYRAMZA and erlotinib required initiation of 3 or more antihypertensive medications compared to 4% of patients treated with placebo and erlotinib.

- Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

**Infusion-Related Reactions (IRR)**, including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. Symptoms of IRR 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. In 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from <1-9%. Grade 3-5 IRR incidence was <1%.

- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

**Worsening of Pre-existing Hepatic Impairment** - Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepaticorenal 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 benefit of treatment is judged to outweigh the risks of clinical deterioration.

- Based on safety data from REACH-2, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of hepatic encephalopathy and hepaticorenal syndrome was higher for patients who received CYRAMZA (6%) compared to patients who received placebo (0%).

**Posterior Reversible Encephalopathy Syndrome (PRES)**, also known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS), has been reported in <0.1% of 2137 patients with various cancers treated with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension.

- Permanently discontinue CYRAMZA in patients who develop PRES. Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

**Proteinuria Including Nephrotic Syndrome** - In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-34%. Grade ≥3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%.

- Monitor for proteinuria. 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.

**Thyroid Dysfunction** - In 2137 patients with various cancers treated with CYRAMZA, the incidence of Grade 1-2 hypothyroidism ranged from <1-3%; there were no reports of Grade 3-5 hypothyroidism. Monitor thyroid function during treatment with CYRAMZA.

**Embryo-Fetal Toxicity** - CYRAMZA can cause fetal harm when administered to pregnant women. 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 3 months after the last dose.

**Lactation** - Because of the potential risk for serious adverse reactions in breastfed children from ramucirumab, advise women not to breastfeed during treatment with CYRAMZA and for 2 months after the last dose.

**Adverse Reactions**

** REGARD:**
- The most common adverse reactions (all Grades) observed in single agent CYRAMZA-treated gastric cancer patients at a rate of ≥5% and >2% higher than placebo were hypertension (16% vs 8%), diarrhea (14% vs 9%), headache (9% vs 3%), and hyponatremia (6% vs 2%).
- The most common serious adverse reactions with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in ≥1% and >5% of CYRAMZA-treated patients in REGARD were: neutropenia (4.7%), epistaxis (4.7%), rash (4.2%), intestinal obstruction (2.1%), and arterial thromboembolic events (1.7%).
- 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 IRR.
- In REGARD, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in REGARD was 0.8% and the rate of IRR was 0.4%.

Please see Important Safety Information continued on pages 18-19 and full Prescribing Information for CYRAMZA.
Important Safety Information for CYRAMZA® (ramucirumab), Continued

RAINBOW:
- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with paclitaxel at a rate of ≥5% and ≥2% higher than placebo with paclitaxel were fatigue/asthenia (57% vs 44%), neutropenia (54% vs 32%), hypertension (25% vs 23%), epistaxis (31% vs 7%), peripheral edema (25% vs 14%), stomatitis (20% vs 7%), proteinuria (17% vs 6%), thrombocytopenia (13% vs 6%), hypoalbuminemia (11% vs 5%), and gastrointestinal hemorrhage events (10% vs 6%).
- The most common serious adverse reactions with CYRAMZA with paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of patients receiving CYRAMZA with paclitaxel were sepsis (3.1%), including 5 fatal events, and gastrointestinal perforations (1.2%), including 1 fatal event.

REVEL:
- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with docetaxel at a rate of ≥5% and ≥2% higher than placebo with docetaxel were neutropenia (55% vs 46%), fatigue/asthenia (55% vs 50%), stomatitis/mucosal inflammation (37% vs 19%), epistaxis (19% vs 7%), febrile neutropenia (16% vs 10%), peripheral edema (16% vs 9%), thrombocytopenia (13% vs 5%), lacrimation increased (13% vs 5%), and hypertension (11% vs 5%).
- 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 with docetaxel compared to 6% overall incidence and 1% for Grade ≥3 pulmonary hemorrhage for placebo with 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 with docetaxel compared to 12% overall incidence and 2% for Grade ≥3 pulmonary hemorrhage for placebo with docetaxel.
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA with docetaxel-treated patients (9%) than in placebo with docetaxel-treated patients (6%). The most common adverse reactions leading to treatment discontinuation in CYRAMZA were IRR (0.5%) and epistaxis (0.3%).

RAISE:
- Thyroid-stimulating hormone (TSH) levels were evaluated in 224 patients (115 CYRAMZA with FOLFIRI-treated patients and 109 placebo with FOLFIRI-treated patients) with normal baseline TSH levels. Increased TSH levels were observed in 53 (44%) patients treated with CYRAMZA with FOLFIRI compared with 4 (4%) patients treated with placebo with FOLFIRI.
- For patients with normal baseline TSH levels treated with CYRAMZA with FOLFIRI, 11% (vs 6%) of patients had increased TSH levels at any time during treatment. For patients with normal baseline TSH levels treated with placebo with FOLFIRI, 6% (vs 5%) of patients had increased TSH levels at any time during treatment.

RAISE-2:
- The most common adverse reactions (all Grades) observed in single agent CYRAMZA-treated HCC patients at a rate of ≥10% and ≥2% higher than placebo were fatigue (36% vs 26%), peripheral edema (25% vs 14%), hypertension (25% vs 13%), abdominal pain (25% vs 16%), decreased appetite (23% vs 20%), proteinuria (20% vs 4%), nausea (19% vs 12%), ascites (18% vs 7%), headache (14% vs 5%), epistaxis (14% vs 3%), insomnia (11% vs 4%), pyrexia (10% vs 3%), vomiting (10% vs 7%), and back pain (10% vs 7%).
- The most common serious adverse reactions with CYRAMZA were ascites (3%) and pneumonia (3%).
- Treatment discontinuations due to adverse reactions occurred in 18% of CYRAMZA-treatment patients, with proteinuria being the most frequent (2%).
- Clinically relevant adverse reactions reported in ≥1% and <10% of CYRAMZA-treated patients in REACH-2 were IRR (9%), hepatic encephalopathy (5%) including 1 fatal event, and hepatorenal syndrome (2%) including 1 fatal event.

RAISE:
- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with FOLFIRI at a rate of ≥5% and ≥2% higher than placebo with FOLFIRI were diarrhea (60% vs 51%), neutropenia (59% vs 46%), decreased appetite (37% vs 27%), epistaxis (33% vs 15%), stomatitis (31% vs 21%), thrombocytopenia (28% vs 14%), hypertension (26% vs 9%), peripheral edema (20% vs 9%), proteinuria (17% vs 5%), palmar-plantar erythrodysesthesia syndrome (13% vs 3%), gastrointestinal hemorrhage events (12% vs 7%), and hypalbuninemia (6% vs 2%). Twenty percent of patients treated with CYRAMZA with FOLFIRI received granulocyte colony-stimulating factors.
- The most common serious adverse reactions with CYRAMZA with FOLFIRI were diarrhea (3.6%), intestinal obstruction (3.0%), and febrile neutropenia (2.8%).
- Treatment discontinuation of any study drug due to adverse reactions occurred more frequently in CYRAMZA with FOLFIRI-treated patients (29%) than in placebo with FOLFIRI-treated patients (13%). The most common adverse reactions leading to discontinuation of any component of CYRAMZA with FOLFIRI as compared to placebo with FOLFIRI were neutropenia (12.5% vs 5.3%) and thrombocytopenia (4.2% vs 0.8%). The most common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (1.5%), and gastrointestinal perforation (1.7%).
- Clinically relevant adverse reaction reported in ≥1% and <5% of patients receiving CYRAMZA with FOLFIRI was gastrointestinal perforation (1.7%), including 4 fatal events.
- Thyroid-stimulating hormone (TSH) levels were evaluated in 224 patients (115 CYRAMZA with FOLFIRI-treated patients and 109 placebo with FOLFIRI-treated patients) with normal baseline TSH levels. Increased TSH levels were observed in 53 (44%) patients treated with CYRAMZA with FOLFIRI compared with 4 (4%) patients treated with placebo with FOLFIRI.

RAISE-2:
- The most common adverse reactions (all Grades) observed in single agent CYRAMZA-treated HCC patients at a rate of ≥10% and ≥2% higher than placebo were fatigue (36% vs 26%), peripheral edema (25% vs 14%), hypertension (25% vs 13%), abdominal pain (25% vs 16%), decreased appetite (23% vs 20%), proteinuria (20% vs 4%), nausea (19% vs 12%), ascites (18% vs 7%), headache (14% vs 5%), epistaxis (14% vs 3%), insomnia (11% vs 4%), pyrexia (10% vs 3%), vomiting (10% vs 7%), and back pain (10% vs 7%).
- The most common serious adverse reactions with CYRAMZA were ascites (3%) and pneumonia (3%).
- Treatment discontinuations due to adverse reactions occurred in 18% of CYRAMZA-treated patients, with proteinuria being the most frequent (2%).
- Clinically relevant adverse reactions reported in ≥1% and <10% of CYRAMZA-treated patients in REACH-2 were IRR (9%), hepatic encephalopathy (5%) including 1 fatal event, and hepatorenal syndrome (2%) including 1 fatal event.

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Please see full Prescribing Information for CYRAMZA.

Reference
**ADVANCED OR METASTATIC GASTRIC OR GEJ ADENOCARCINOMA**

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

**META**

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**SELECT IMPORTANT SAFETY INFORMATION**

**Hemorrhage**
- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown.
- Patients with NSCLC receiving therapeutic anticoagulation or with evidence of major airway invasion by cancer were excluded from REVEL. In addition, patients with NSCLC with a recent history of gross hemoptysis, those receiving 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 cavitition were excluded from REVEL and RELAY; therefore the risk of pulmonary hemorrhage in these groups of patients is unknown.
- Permanently discontinue CYRAMZA in patients who experience severe [Grade 3 or 4] bleeding.

**Please see Important Safety Information on pages 16-19 and full Prescribing Information for CYRAMZA.**

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