Effective Date: 11/01/2018

Cyramza® (ramucirumab)

FDA approval: April 21, 2014  
HCPCS: J9308  
Benefit: Medical

Policy/Criteria:

Note: Requests must be supported by submission of chart notes and patient specific documentation.

I. Coverage Criteria:

A. Coverage of the requested drug is provided when all criteria below are met:
   a) Prescriber is an oncologist
   b) Diagnosis of gastric cancer or gastroesophageal junction adenocarcinoma
      i. Documented ECOG performance status of 0 to 2
      ii. Experienced disease progression during or after first-line fluoropyrimidine- or platinum-containing chemotherapy
      iii. Will be used as monotherapy OR in combination with paclitaxel

OR

c) Diagnosis of metastatic non-small cell lung cancer (NSCLC)
   i. Documented ECOG performance status of 0 to 2
   ii. Experienced disease progression during or after first-line platinum-based chemotherapy
   iii. Will be used in combination with docetaxel at appropriate dosing
   iv. If the patient has an EGFR or ALK genomic tumor aberration, disease progression following FDA-approved therapy for the aberration is required

OR

d) Diagnosis of metastatic colorectal cancer (mCRC)
   i. Documented ECOG performance status of 0 to 2
   ii. Experienced disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine
   iii. Will be used in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil) or irinotecan alone for those who are intolerant to, have experienced toxicity to, or have a contraindication to 5-fluorouracil
   iv. Must have not received prior irinotecan-based therapy

B. Quantity Limitations, Authorization Period and Renewal Criteria

a) Gastric cancer or gastroesophageal junction adenocarcinoma

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i. Quantity Limit:
   1. 8 mg/kg every 14 days
ii. Authorization period: 6 months initially, annually thereafter

b) Non-small cell lung cancer
i. Quantity limit:
   1. 10 mg/kg on day 1 of a 21-day cycle
ii. Authorization period: 6 months initially, 6 months thereafter

c) Colorectal cancer
i. Quantity limit:
   1. 8 mg/kg every 14 days
ii. Authorization period: 6 months initially, 6 months thereafter

d) Renewal Criteria:
   i. Continuation of therapy authorized until disease progression or intolerable toxicity occurs

C. Cyramza is considered investigational when used for all other conditions, including but not limited to:
   a) Hepatocellular carcinoma
   b) Breast cancer
   c) Ovarian cancer

***Note: Coverage may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at [http://www.cms.hhs.gov/](http://www.cms.hhs.gov/). Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Therapeutic considerations:

A. FDA approved indication / Diagnosis
   a. Cyramza is a human vascular endothelial growth factor inhibitor receptor 2 antagonist indicated
   i. 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.
   ii. 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.
   iii. 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.

*Please refer to most recent prescribing information.

B. Background Information
   i. Eastern Cooperative Oncology Group (ECOG) Performance Score (PS)
      1. 2015 NCCN guidelines for gastric cancer, colon cancer, and NSCLC support use of chemotherapy in patients with metastatic disease with performance status 0-2.
   ii. Gastric cancer
      1. Gastric cancer is the fifth most common malignancy and the third leading cause of cancer mortality worldwide.\(^1\) Incidence in the US is relatively low; an estimated 22,220 diagnoses and 10,990 deaths will be attributed to the disease in 2014.\(^2\) Risk factors include Helicobacter pylori (H. pylori) infection, smoking, high salt intake, and heavy alcohol consumption.
2. Cyramza (ramucirumab) is a fully human vascular endothelial growth factor receptor-2 (VEGFR-2) antagonist believed to reduce tumor growth and vascularity in gastric adenocarcinomas.³

3. Currently, platinum-based and fluoropyrimidine-based combinations are accepted worldwide as established first-line drug regimens.¹ Cyramza is indicated for use after disease progression on or following fluoropyrimidine (infusional fluorouracil or capecitabine) or platinum-containing chemotherapy. It was the first FDA-approved second-line treatment for gastric cancer.³

4. Efficacy was established in the REGARD and RAINBOW clinical trials. Cyramza produced better results when combined with paclitaxel (RAINBOW trial) than it did as a single agent (REGARD trial); therefore, Cyramza in combination with paclitaxel is preferred.

5. REGARD showed a significant median survival benefit of 1.4 months vs. best supportive care (5.2 months vs. 3.8 months). RAINBOW showed treatment with Cyramza plus paclitaxel was associated with a median overall survival of 9.6 months, compared to 7.4 months for the placebo + paclitaxel arm.

iii. Non-small cell lung cancer

1. Lung cancer is the leading cause of cancer death in the United States. In 2014, there will be an estimated 224,210 new cases and 159,260 deaths due to the disease. The disease is divided into 2 major classes: NSCLC and small cell lung cancer. NSCLC accounts for more than 85% of all lung cancer cases, and it includes two major types: 1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types); and 2) squamous cell (epidermoid) carcinoma. Leading risk factors include tobacco smoke, radon gas, and asbestos.⁴

2. Cyramza binds to the VEGFR-2 domain, preventing all VEGF ligand binding and receptor activation. Blockade of VEGFR-2 inhibits formation, proliferation, and migration of new blood vessels to cancer cells.⁵

3. Initial therapy usually consists of four to six cycles of platinum-based chemotherapy, with some patients receiving maintenance therapy. Although 30-40% of patients initially respond to cytotoxic therapy, all patients eventually have disease progression on or after treatment. Patients with an EGFR or ALK genomic tumor aberration should receive targeted therapy (TKIs), but most patients do not have mutations associated with approved targeted drugs.

4. The REVEL study assessed efficacy and safety of Cyramza + docetaxel versus placebo + docetaxel as second-line therapy in patients with metastatic NSCLC whose disease had progressed during or after first-line platinum-based chemotherapy with or without maintenance treatment. Median overall survival (OS) was 10.5 months for Cyramza + docetaxel and 9.1 months for placebo + docetaxel (p = 0.023). Median progression-free survival was 4.5 months for Cyramza compared with 3.0 months for the control group (p < 0.0001). Cyramza is the first therapy for previously treated NSCLC to improve OS compared with an active comparator.

iv. Colorectal cancer

1. Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. Current estimated rates of colorectal cancer are approximately 95,000 new colon cancer cases per year and 40,000 new cases of rectal cancer. Approximately 50-60% of patients will develop metastatic disease.

2. NCCN recommendations for initial therapy for metastatic colorectal cancer include: FOLFOX, FOLFIRI, CapeOx, infusional 5-FU/LV or capecitabine, or FOLFOXIRI with or without Avastin. Avastin may be added to the regimen after first progression if not included as initial therapy. Most regimens contain oxaliplatin and a fluoropyrimidine. However, oxaliplatin is not included in all initial treatment regimen options.

3. Efficacy was established in the RAISE study. Participants had disease progression on or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. 1072 patients were randomized 1:1 to receive Cyramza 8 mg/kg or placebo, in combination with FOLFIRI. Treatment cycles were repeated every 2 weeks. Median overall survival and progression-free survival were...
statistically significantly improved in the Cyramza arm (median OS: 13.3 months) vs. placebo arm (median OS: 11.7 months).

4. Claim: Cyramza is the first VEGF inhibitor to show benefit after disease progression with first-line Avastin and validates the approach of VEGF receptor blockade to improve survival of patients with metastatic colorectal cancer.

5. NCCN guidelines for colorectal cancer expand the accepted use of Cyramza beyond the labeled indication. However, Avastin is preferred over Cyramza and Zaltrap, based on toxicity and cost. Because of this, and the modest improvement in overall survival, the Plan will provide coverage for the population for which efficacy has been proven in clinical trials.

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<th>Cross References</th>
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<tbody>
<tr>
<td>Drug Review</td>
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<td>Therapies in Metastatic Non-Small Cell Lung Cancer – 11/9/17 P&amp;T</td>
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</tbody>
</table>

C. Efficacy

*Please refer to most recent prescribing information.

D. Medication Safety Considerations

Box Warning: Yes
Hemorrhage, Gastrointestinal Perforation, Impaired Wound Healing

*Please refer to most recent prescribing information.

E. Dosing and administration

a. Dosing:
   i. Gastric cancer
      1. 8 mg/kg every 2 weeks administered as an IVI over 60 minutes
   ii. Non-small cell lung cancer
      1. 10 mg/kg administered by IVI over approximately 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion
   iii. Colorectal cancer
      1. 8 mg/kg every 2 weeks administered by IVI over 60 minutes prior to FOLFIRI administration
   iv. Continue Cyramza until disease progression or unacceptable toxicity.

*Please refer to most recent prescribing information.

F. How supplied

a. Single-dose vials:
   i. 100 mg/10 mL (10 mg/mL)
   ii. 500 mg/50 mL (10 mg/mL)

References:


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6. Cyramza™ injection, for intravenous use [prescribing information]. Indianapolis, IN: Eli Lilly; April 2015.


### Policy History

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<th>#</th>
<th>Date</th>
<th>Change Description</th>
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<tbody>
<tr>
<td>1.0</td>
<td>Effective Date: 08/14/2014</td>
<td>New Drug Document</td>
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<tr>
<td>1.1</td>
<td>Effective Date: 12/11/2014</td>
<td>Updated for gastric cancer indication with paclitaxel.</td>
</tr>
<tr>
<td>1.2</td>
<td>Effective Date: 05/07/2015</td>
<td>Updated to include non-small cell lung cancer indication. Updated template.</td>
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<tr>
<td>1.3</td>
<td>Effective Date: 08/13/2015</td>
<td>Updated to include mCRC indication.</td>
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<tr>
<td>1.4</td>
<td>Effective Date: 11/10/2016</td>
<td>Annual Review. No criteria changes. Document template updated.</td>
</tr>
<tr>
<td>1.5</td>
<td>Effective Date: 11/09/2017</td>
<td>Annual Review of Medical Policy</td>
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<tr>
<td>1.6</td>
<td>Effective Date: 11/01/2018</td>
<td>Criteria update per oncology vendor</td>
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*The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or [http://dailymed.nlm.nih.gov/dailymed/index.cfm](http://dailymed.nlm.nih.gov/dailymed/index.cfm)*