Blue Cross Blue Shield Blue Care Network of Michigan

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P&T Date: 04/10/2025

Cyramza® (ramucirumab)

HCPCS: J9308

Policy:

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

Note: This policy pertains to Medicare Part B only

A. Coverage of the requested drug is provided when all the following are met:
   a. Prescribed by or in consultation with 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
      AND
      iii. Will be used in combination with docetaxel at appropriate dosing
      AND
      iv. If the patient has an EGFR or ALK genomic tumor aberration, disease progression following FDA-approved therapy for the aberration is required
      OR
      v. Being used as first-line therapy
      AND
      vi. Will be used in combination with erlotinib
      AND
      vii. The tumor has epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations
      OR
   d. Diagnosis of metastatic colorectal cancer (mCRC)
      i. Documented ECOG performance status of 0 to 2

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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-flourouracil
iv. Must not have received prior irinotecan-based therapy
OR

e. Diagnosis of hepatocellular carcinoma
i. Will be used as monotherapy
ii. Must have an alpha-fetoprotein level ≥ 400 ng/mL
iii. ECOG performance status of 0 to 1
iv. Must have had previous treatment with sorafenib

B. Quantity Limitations, Authorization Period and Renewal Criteria
a. Quantity Limits: Align with FDA recommended dosing
b. Authorization Period: Aligns with FDA recommended or guideline supported treatment duration and provided for at least 60 days and up to 6 months at a time
c. Renewal Criteria: Continuation of therapy until disease progression or unacceptable toxicity occurs

***Note: Coverage and approval duration 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/. 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.

Background Information:

- Cyramza is a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist indicated:

  - As a single agent or in combination with paclitaxel for treatment of advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy

  - In combination with erlotinib for first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations

  - 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

  - 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

  - As a single agent for the treatment of hepatocellular carcinoma (HCC) in patients who have an alpha fetoprotein of ≥ 400 ng/mL and have been treated with sorafenib

- Gastric or Gastroesophageal Junction Adenocarcinoma

  - Efficacy was established in the REGARD and RAINBOW clinical trials. Both trials excluded patients with an ECOG performance score greater than 2. Cyramza produced better results when combined with paclitaxel

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(RAINBOW trial) than it did as a single agent (REGARD trial). Therefore, Cyramza in combination with paclitaxel is preferred but it can be used as a single agent as well. REGARD showed a significant median survival benefit of 1.4 months vs. best supportive care. 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.

- Metastatic Non-Small Cell Lung Cancer

    - National Comprehensive Cancer Network (NCCN) 2025 guidelines for non-small cell lung cancer state initial therapy in most instances should consist of four to six cycles of platinum-based chemotherapy, with some patients receiving maintenance therapy. In addition, patients with an EGFR or ALK genomic tumor aberration should receive targeted therapy (TKIs) as well prior to initiation of Cyramza.

    - 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. The study excluded patients with an ECOG performace score greater than 2. 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 ($p < 0.0001$).

    - The efficacy of Cyramza in combination with erlotinib was evaluated in the RELAY trial, a randomized, double-blind, placebo-controlled, multicenter study of 449 patients with previously untreated metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) substitution mutations. The study excluded patients with an ECOG performance score greater than 1. The primary endpoint was progression free survival (PFS). Progression free survival was significantly longer in the ramucirumab plus erlotinib group (19.4 months [95% CI 15.4 – 21.6]) than in the placebo plus erlotinib group (12.4 months [11.0–13.5]), with a stratified hazard ratio of 0.59 (95% CI 0.46 – 0.76; $p < 0.0001$).

- Metastatic Colorectal Cancer

    - NCCN 2024 guidelines for colon cancer recommend FOLFOX, FOLFIRI, CapeOx, infusional 5-FU/LV, capecitabine, or FOLFOXIRI with or without Avastin as first line therapy. 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. Guidelines do not allow use of Cyramza when irinotecan was used in a prior line of therapy.

    - The RAISE study assessed efficacy and safety of Cyramza + FOLFIRI versus placebo in 1072 patients who experienced disease progression on or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Patients were excluded if they had an ECOG performance score greater than 2. 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).

- Hepatocellular Carcinoma

    - Efficacy was evaluated in REACH-2, a multinational, randomized, double-blind, placebo-controlled, multicenter study in patients with advanced HCC with AFP ≥ 400 ng/mL who had disease progression on or after prior sorafenib therapy or who were intolerant to sorafenib. Two hundred ninety-two patients were randomized 1:1 to receive Cyramza 8 mg/kg or placebo every 2 weeks. Patients were excluded if they had an ECOG performance score greater than 1. Median overall survival and progression-free survival were

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statistically significantly improved in the Cyramza arm (median OS: 8.5 months) vs. placebo arm (median OS: 7.3 months).

References:

1. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomized phase 3 trial. *Lancet Oncol.* 2013; 15: 1224-35.
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4. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (Version 3.2025). 2025 Jan 14. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed on February 7, 2025.
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12. National Comprehensive Cancer Network. Hepatocellular Carcinoma (Version 4.2024). 2025 Jan 10. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf. Accessed on February 7, 2025.
13. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet. 2019 Dec 1; 20 (12): 1655 – 1669.

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<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>2.7</td><td>Effective Date: 04/10/2025</td><td>Annual review of criteria was performed, no changes were made</td></tr>
<tr><td>2.6</td><td>Effective Date: 04/11/2024</td><td>Annual review of criteria was performed, no changes were made</td></tr>
<tr><td>2.5</td><td>Effective Date: 04/06/2023</td><td>Updated approval length to allow for no less than a 60 day approval</td></tr>
<tr><td>2.4</td><td>Effective Date: 08/04/2022</td><td>Updated approval length to allow for FDA recommended dosing or up to 6 months at a time</td></tr>
<tr><td>2.3</td><td>Effective Date: 08/12/2021</td><td>Annual review – no changes to the criteria</td></tr>
<tr><td>2.2</td><td>Effective Date: 12/01/2020</td><td>UM medical management system update for BCBS
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
<tr><td>2.1</td><td>Effective Date: 08/13/2020</td><td>Updated to include new indication for first-line therapy in combination with erlotinib in NSCLC</td></tr>
<tr><td>2.0</td><td>Effective Date: 08/15/2019</td><td>Added new indication of hepatocellular carcinoma</td></tr>
<tr><td>1.9</td><td>Effective Date: 02/01/2019</td><td>UM medical management system update for MAPPO
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<tr><td>1.8</td><td>Effective Date: 11/01/2018</td><td>Criteria update per oncology vendor</td></tr>
<tr><td>1.7</td><td>Effective Date: 11/09/2017</td><td>Annual Review of Medical Policy</td></tr>
<tr><td>1.6</td><td>Effective Date: 01/01/2017</td><td>UM medical management system update for BCNA
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<tr><td>1.5</td><td>Effective Date: 11/10/2016</td><td>Annual Review of Medical Policy, No criteria changes and Document template updated</td></tr>
<tr><td>1.4</td><td>Effective Date: 08/13/2015</td><td>Updated to include mCRC indication.</td></tr>
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<tr><td>1.3</td><td>Effective Date: 05/07/2015</td><td>Updated to include non-small cell lung cancer indication. Updated template.</td></tr>
<tr><td>1.2</td><td>Effective Date: 04/01/2015</td><td>UM medical management system update for BCN
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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>1.0</td><td>Effective Date: 08/14/2014</td><td>New Drug Document
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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.*

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