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Effective Date: 04/11/2024

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-fluorouracil
- 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) 2022 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 performance 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 2022 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

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

References:

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3. Fuchs C, Tomasek J, Yong C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomized, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2014; 383: 31-39.
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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.

Policy History												
#	Date	Change Description										
2.6	Effective Date: 04/11/2024	Annual review of criteria was performed, no changes were made										
2.5	Effective Date: 04/06/2023	Updated approval length to allow for no less than a 60 day approval										
2.4	Effective Date: 08/04/2022	Updated approval length to allow for FDA recommended dosing or up to 6 months at a time										
2.3	Effective Date: 08/12/2021	Annual review – no changes to the criteria										
2.2	Effective Date: 12/01/2020	UM medical management system update for BCBS <table border="1" data-bbox="467 541 1344 751"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <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> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	Yes	BCNA	Yes
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2.1	Effective Date: 08/13/2020	Updated to include new indication for first-line therapy in combination with erlotinib in NSCLC										
2.0	Effective Date: 08/15/2019	Added new indication of hepatocellular carcinoma										
1.9	Effective Date: 02/01/2019	UM medical management system update for MAPPO <table border="1" data-bbox="467 961 1344 1171"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>No</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> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	No	BCN	Yes	MAPPO	Yes	BCNA	Yes
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1.8	Effective Date: 11/01/2018	Criteria update per oncology vendor										
1.7	Effective Date: 11/09/2017	Annual Review of Medical Policy										
1.6	Effective Date: 01/01/2017	UM medical management system update for BCNA <table border="1" data-bbox="467 1392 1344 1602"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>No</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>No</td> </tr> <tr> <td>BCNA</td> <td>Yes</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	No	BCN	Yes	MAPPO	No	BCNA	Yes
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1.5	Effective Date: 11/10/2016	Annual Review of Medical Policy, No criteria changes and Document template updated										
1.4	Effective Date: 08/13/2015	Updated to include mCRC indication.										
1.3	Effective Date: 05/07/2015	Updated to include non-small cell lung cancer indication. Updated template.										

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1.2	Effective Date: 04/01/2015	UM medical management system update for BCN <table border="1" data-bbox="467 205 1344 411"> <thead> <tr> <th data-bbox="467 205 943 268">Line of Business</th> <th data-bbox="943 205 1344 268">PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td data-bbox="467 268 943 306">BCBS</td> <td data-bbox="943 268 1344 306">No</td> </tr> <tr> <td data-bbox="467 306 943 344">BCN</td> <td data-bbox="943 306 1344 344">Yes</td> </tr> <tr> <td data-bbox="467 344 943 382">MAPPO</td> <td data-bbox="943 344 1344 382">No</td> </tr> <tr> <td data-bbox="467 382 943 411">BCNA</td> <td data-bbox="943 382 1344 411">No</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	No	BCN	Yes	MAPPO	No	BCNA	No
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1.1	Effective Date: 12/11/2014	Updated for gastric cancer indication with paclitaxel.										
1.0	Effective Date: 08/14/2014	New Drug Document <table border="1" data-bbox="467 569 1344 779"> <thead> <tr> <th data-bbox="467 569 943 632">Line of Business</th> <th data-bbox="943 569 1344 632">PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td data-bbox="467 632 943 669">BCBS</td> <td data-bbox="943 632 1344 669">No</td> </tr> <tr> <td data-bbox="467 669 943 707">BCN</td> <td data-bbox="943 669 1344 707">No</td> </tr> <tr> <td data-bbox="467 707 943 745">MAPPO</td> <td data-bbox="943 707 1344 745">No</td> </tr> <tr> <td data-bbox="467 745 943 779">BCNA</td> <td data-bbox="943 745 1344 779">No</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	No	BCN	No	MAPPO	No	BCNA	No
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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>.