Policy Name	Policy Number	Scope
Ramucirumab (Cyramza®)	MP-RX-FP-20-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of *Ramucirumab (Cyramza®),* a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist approved by the Food and Drug Administration (FDA) for the treatment of certain patients with advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma, metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations, metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy, metastatic colorectal cancer, and hepatocellular carcinoma.

Background Information

Cyramza is FDA approved, as a single agent or in combination with paclitaxel, to treat gastric or gastro-esophageal junction adenocarcinoma which has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy. The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Cyramza in esophageal adenocarcinoma similar to the FDA approved use in gastric cancer.

Cyramza is also FDA approved to treat non-small cell lung cancer (NSCLC) in combination with docetaxel for those with disease progression on or after platinum-based chemotherapy. The labeled indication also notes that those with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA approved therapies for these aberrations prior to receiving Cyramza. Since approval for this indication, numerous other actionable mutations with FDA approved therapies have emerged. As a result, NCCN algorithm for NSCLC recommends patients with actionable mutations should receive targeted therapy for these mutations first, then (if needed) proceed to general systemic therapy including platinum-based therapy, then (if needed) proceed to Cyramza plus docetaxel. Cyramza also recently received FDA approval in combination with erlotinib as first line therapy for EGFR mutated NSCLC based on results of the RELAY trial (Nakagawa 2019).

Cyramza is FDA approved to treat metastatic colorectal cancer (mCRC) in combination with FOLFIRI regimen in those who progress after bevacizumab-, oxaliplatin-, and fluoropyrimidine-containing chemotherapy (i.e. FOLFOX/CAPEOX + bevacizumab). NCCN recommends Cyramza as an option after any oxaliplatin-based therapy, as well as after fluoropyrimidine regimens without oxaliplatin, regardless of previous bevacizumab use. However, NCCN notes that bevacizumab is the preferred anti-antiangiogenic agent and recognizes that Cyramza was studied after first-line therapy with fluoropyrimidine/oxaliplatin/bevacizumab (Tabernero 2015). NCCN

notes that no data exists that suggest activity of FOLFIRI plus Cyramza in individuals who have progressed on FOLFIRI plus bevacizumab.

Cyramza recently received FDA approval for the treatment of advanced or unresectable hepatocellular carcinoma as subsequent treatment for progressive disease after sorafenib treatment, in patients with serum α–fetoprotein (AFP) concentrations of ≥ 400 ng/mL. The approval is based on the REACH (Zhu 2015) and REACH 2 (Zhu 2019) studies. The REACH study, which did not result in improved overall survival (OS) compared to placebo, included patients with any AFP level. However, subgroup analysis around baseline AFP level prompted the REACH 2 study which included only patients with baseline AFP of ≥ 400 ng/mL. In this study, the primary endpoint of improved median overall survival was statistically significant.

Cyramza has also shown benefit in urothelial carcinoma. While neither the FDA nor NCCN have endorsed Cyramza for this indication, the RANGE study (Petrylak 2017) indicated that participants treated with ramucirumab plus docetaxel experienced longer PFS compared with placebo plus docetaxel in select individuals with platinum-refractory advanced or metastatic urothelial carcinoma. Individuals in this study had received no more than one immune checkpoint inhibitor or prior systemic chemotherapy regimen and no prior systemic taxane therapy..

Definitions and Measures:

- Actionable molecular markers include EGFR, ALK, ROS1, BRAF, NTRK, MET and RET mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NCCN 1, 2A).
- Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).
- Disease Progression/ Progressive Disease (PD): Cancer that is growing, spreading, or getting worse.
- ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:
    - 0 = Fully active, able to carry on all pre-disease performance without restriction
    - 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
    - 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
    - 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
    - 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

Policy Name	Policy Number	Scope
Ramucirumab (Cyramza®)	MP-RX-FP-20-23	☒ MMM MA ☒ MMM Multihealth

- 5 = Dead

- Fluoropyrimidine: A type of antimetabolite used to treat cancer. Examples include capecitabine, floxuridine, and fluorouracil (5-FU).
- Non-small cell lung cancer: A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.
- Refractory Disease: Illness or disease that does not respond to treatment.
- Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.
- Taxane: A type of mitotic inhibitor and antimicrotubule drug used to treat cancer that blocks cell growth by stopping mitosis (cell division).
- Unresectable: Unable to be removed with surgery.
- Urothelial carcinoma: A type of bladder cancer which occurs in the urinary tract system.
- Vascular endothelial growth factor (VEGF): A substance made by cells that stimulates new blood vessel formation.

Approved Indications

FDA-approved indications for Cyramza include:

A. 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.
B. 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.
C. In combination with docetaxel, for treatment of metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy. In this setting, patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Cyramza.
D. 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.
E. As a single agent, for the treatment of hepatocellular carcinoma in patients who have an alpha fetoprotein of ≥400 ng/mL and have been treated with sorafenib.

Other Uses

i. NCCN and other compendia do not support the use of Cyramza in breast cancer, metastatic melanoma, ovarian, fallopian tube or primary peritoneal cancer, pleural mesothelioma, or renal cell cancer.

Policy Name	Policy Number	Scope
Ramucirumab (Cyramza®)	MP-RX-FP-20-23	☒ MMM MA ☒ MMM Multihealth

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9308	Injection, ramucirumab, 5 mg [Cyramza]

ICD-10	Description
C15.3-C15.9	Malignant neoplasm of esophagus
C16.0-C16.9	Malignant neoplasm of stomach
C18.0-C20	Malignant neoplasm of colon, rectosigmoid junction, rectum
C22.0	Hepatocellular carcinoma
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C45.0	Mesothelioma of pleura
C45.2	Mesothelioma of pericardium
C45.7	Mesothelioma of other sites (when specified as tunica vaginalis testis mesothelioma)
C65.1-C65.9	Malignant neoplasm of renal pelvis
C66.1-C66.9	Malignant neoplasm of ureter
C67.0-C67.9	Malignant neoplasm of bladder
C68.0	Malignant neoplasm of urethra
C78.00-C78.02	Secondary malignant neoplasm of lung
C78.5	Secondary malignant neoplasm of large intestine and rectum
C78.89	Secondary malignant neoplasm of other digestive organs
Z85.01	Personal history of malignant neoplasm of esophagus
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.51	Personal history of malignant neoplasm of bladder
Z85.53-Z85.59	Personal history of malignant neoplasm of renal pelvis, ureter, other urinary tract organ

Policy Name	Policy Number	Scope
Ramucirumab (Cyramza®)	MP-RX-FP-20-23	☒ MMM MA ☒ MMM Multihealth

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Ramucirumab (Cyramza®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Individual has a diagnosis of *Hepatocellular Carcinoma* and the following are met:
   A. Individual has inoperable or metastatic disease (NCCN 1); **AND**
   B. Individual has had disease progression on or after prior treatment with Sorafenib; **AND**
   C. Ramucirumab is used as a single agent; **AND**
   D. Individual has a baseline serum α–fetoprotein (AFP) concentrations of ≥ 400 ng/mL at initiation of therapy;
   E. Individual has a Child-Pugh Class A score;

OR

ii. Individual has a diagnosis of *Esophageal, Gastric, or Gastroesophageal Junction Adenocarcinoma* and the following are met:
   A. Individual has advanced (non-resectable) or metastatic disease; **AND**
   B. Ramucirumab is used as a single agent or in combination with paclitaxel, or in combination with irinotecan; **AND**
   C. Individual has had disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy;

OR

iii. Individual has a diagnosis of *metastatic Non-small Cell Lung Cancer (NSCLC)* and the following are met (Label, NCCN 2A):
   A. Ramucirumab is used in combination with docetaxel; **AND**
   B. Individual meets either of the following:
      1. Individual does not have presence of actionable molecular markers*, *and* the disease has progressed on or after platinum-containing chemotherapy;
      OR
      2. Individual has presence of actionable molecular markers* and *both* of the following criteria are met:
         a. Disease has progressed on a U.S. Food & Drug Administration (FDA)-approved therapy for these mutations prior to receiving ramucirumab; **AND**

b. Disease has progressed on or after platinum-containing chemotherapy;

***Note:** Actionable molecular markers include EGFR, ALK, ROS1, BRAF, NTRK, MET and RET mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NCCN 1, 2A).

OR

iv. Individual has a diagnosis of *metastatic Non-small Cell Lung Cancer (NSCLC)* and the following are met:

A. Individual has an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation with test results confirmed; **AND**

B. Ramucirumab is used as first line therapy in combination with erlotinib;

OR

v. Individual has a diagnosis of *metastatic Colorectal Cancer* and the following are met:

A. Individual has had disease progression on or after prior bevacizumab- (or bevacizumab biosimilar), oxaliplatin-, and fluoropyrimidine- containing chemotherapy; **AND**

B. Ramucirumab is used in combination with irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI);

OR

C. Individual has proficient mismatch/repair/microsatellite-stable (pMMR/MSS), deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or PLIE/POLD1 mutation (NCCN 2A); **AND**

D. Individual is using in combination with irinotecan or FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil);

OR

vi. Individual has a diagnosis of *Urothelial Cancer* originating from the bladder, urethra, ureter, or renal pelvis and the following are met (Petrylak 2017):

A. Individual is 18 years of age or older; **AND**

B. Ramucirumab is used in combination with docetaxel; **AND**

C. Individual has a current Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; **AND**

D. Individual has locally advanced, unresectable, or metastatic disease that has progressed after platinum-containing chemotherapy (cisplatin or carboplatin); **AND**

E. Individual has received treatment with no more than one immune checkpoint inhibitor (such as, atezolizumab, avelumab, durvalumab, nivolumab or pembrolizumab); **AND**

F. Individual has received treatment with no more than one prior systemic chemotherapy regimen in the relapsed or metastatic setting; **AND**

Policy Name	Policy Number	Scope
Ramucirumab (Cyramza®)	MP-RX-FP-20-23	☒ MMM MA ☒ MMM Multihealth

G. Individual has received no prior systemic taxane therapy in any setting (that is, neoadjuvant, adjuvant, or metastatic).

OR

vii. Individual has a diagnosis of *pleural mesothelioma, pericardial mesothelioma, or tunica vaginalis testis mesothelioma* and the following is met:

A. Individual is using as subsequent therapy; **AND**

B. Individual is using Cyramza in combination with gemcitabine.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Ramucirumab (Cyramza®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of an unacceptable toxicity or disease progression while on the current regimen. The following information should be submitted for reauthorization:

A. A current oncology note documenting the patient's response to treatment showing no progression of disease.

B.Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months

ii. Reauthorization Approval Duration: Up to 6 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. If Ramucirumab is used for colorectal cancer in combination with the same irinotecan-based regimen that was previously used in combination with bevacizumab (or bevacizumab biosimilar);

OR

ii. The following diagnoses:

A. Breast cancer; **OR**

B.Metastatic melanoma; **OR**

C.Ovarian, fallopian tube or primary peritoneal cancer; **OR**

D. Renal cell cancer;

Policy Name	Policy Number	Scope
Ramucirumab (Cyramza®)	MP-RX-FP-20-23	☒ MMM MA ☒ MMM Multihealth

OR

iii. May not be approved if all the above criteria (Section A: Criteria for Initial Approval) have not been met or for all other indications.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Use	Recommended Dosing Schedule
Gastric Cancer	Cyramza 8 mg/kg every 2 weeks as a single agent or in combination with weekly paclitaxel.
Non-Small Cell Lung Cancer	Cyramza 10 mg/kg every 2 weeks with daily erlotinib. Cyramza 10 mg/kg on Day 1 of a 21-day cycle prior to docetaxel.
Colorectal Cancer	Cyramza 8 mg/kg every 2 weeks prior to FOLFIRI.
Hepatocellular Carcinoma	CYRAMZA 8 mg/kg every 2 weeks.
Exceptions	
None	

Reference Information

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3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023; Updated periodically.

5. 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 Oncol 2019; 20:1655-1669.
6. NCCN Clinical Practice Guidelines in Oncology™. © 2019 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp.
    a. Esophageal and Esophagogastric Junction Cancers. V5.2022. Revised December 5, 2022.
    b. Gastric Cancer V2.2022. Revised December 5, 2022.
    c. Non-Small Cell Lung Cancer. V1.2023. Revised December 22, 2022.
    d. Colon Cancer. V2.2022. Revised October 27, 2022.
    e. Rectal Cancer V3.2022. Revised October 27, 202.
    f. Hepatobiliary Cancers. V4.2022. Revised December 9, 2022.
7. Petrylak DP, de Wit R, Chi KN, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial. Lancet. 2017; 390(10109):2266-2277.
8. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol. 2015; 16(5):499-508. Correction: 2015; 16(6):e262.
9. Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015; 16(7):859-870.
10. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019; 20(2):282-296.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy Name	Policy Number	Scope
Ramucirumab (Cyramza®)	MP-RX-FP-20-23	☒ MMM MA ☒ MMM Multihealth

Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Annual Review 11/15/2024	Update colon cancer to include POLE/POLD1 mutation, wording and formatting. Update hepatocellular carcinoma criteria with child-pugh score, add criteria for colorectal cancers pMMR/MSS and dMMR/MSI-H disease and mesothelioma. Add dosage for hepatocellular carcinoma. Minor wording and formatting updates. Coding Reviewed added ICD-10-CM C45.0, C45.2, C45.7.	2/18/2025	3/6/2025
Select Review 2/15/2024	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.	3/25/2024	5/9/2024
Policy Inception 11/15/2023	Elevance Health's Medical Policy adoption.	N/A	11/30/2023