Medical Policy:

Cyramza® (ramucirumab) Intravenous

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.48	March 26, 2025	

The treating physician or primary care provider must submit to EmblemHealth, or ConnectiCare, as applicable (hereinafter jointly referred to as "EmblemHealth"), the clinical evidence that the member meets the criteria for the treatment or surgical procedure. Without this documentation and information, EmblemHealth will not be able to properly review the request preauthorization or post-payment review. The clinical review criteria expressed below reflects how EmblemHealth determines whether certain services or supplies are medically necessary. This clinical policy is not intended to pre-empt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Health care providers are expected to exercise their medical judgment in rendering appropriate care.

EmblemHealth established the clinical review criteria based upon a review of currently available clinical information (including clinical outcome studies in the peer reviewed published medical literature, regulatory status of the technology, evidence-based guidelines of public health and health research agencies, evidence-based guidelines and positions of leading national health professional organizations, views of physicians practicing in relevant clinical areas, and other relevant factors). EmblemHealth expressly reserves the right to revise these conclusions as clinical information changes and welcomes further relevant information. Each benefit program defines which services are covered. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered and/or paid for by EmblemHealth, as some programs exclude coverage for services or supplies that EmblemHealth considers medically necessary.

If there is a discrepancy between this guideline and a member's benefits program, the benefits program will govern. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test or procedure over another. In addition, coverage may be mandated by applicable legal requirements of a state, the Federal Government or the Centers for Medicare & Medicaid Services (CMS) for Medicare and Medicaid members. All coding and web site links are accurate at time of publication.

EmblemHealth may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. EmblemHealth Services Company, LLC, has adopted this policy in providing management, administrative and other services to EmblemHealth Plan, Inc., EmblemHealth Insurance Company, EmblemHealth Services Company, LLC, and Health Insurance Plan of Greater New York (HIP) related to health benefit plans offered by these entities. ConnectiCare, an EmblemHealth company, has also adopted this policy. All of the aforementioned entities are affiliated companies under common control of EmblemHealth Inc.

Definition

Cyramza (ramucirumab) is a vascular endothelial growth factor (VEGF) receptor 2 antagonist that inhibits ligand-stimulated activation of the VEGF receptor 2, ligand-induced proliferation, and migration of human endothelial cells. Unlike all clinically approved angiogenesis inhibitors, the fully human monoclonal antibody ramucirumab, specifically inhibits VEGFR-2.

Length of Authorization

Coverage will be provided for six months and may be renewed.

Dosing Limits [Medical Benefit]

Max Units (per dose and over time):

Gastric/Esophageal/Esophagogastric Junction Cancers, Colorectal Cancer and HCC: 180 billable units every 14 days

NSCLC: 240 billable units every 14 days

Guideline

I. INITIAL CRITERIA

Cyramza (ramucirumab) may be considered medically necessary for the following diagnosis when all of the following criteria are met:

1. **Colon, Rectal, or Appendiceal Cancer**. Approve if the patient meets ALL of the following (A, B, C, D, **AND** E):
    A. Patient is ≥ 18 years of age; **AND**
    B. Patient had advanced or metastatic disease; **AND**
    C. Patient has received BOTH of the following (i **AND** ii):
        i. Oxaliplatin; **AND**
        ii. Fluoropyrimidine (e.g., 5-fluorouracil [5-FU], capecitabine); **AND**
    D. Cyramza will be used in combination with ONE of the following (i **OR** ii):
        i. Irinotecan; **OR**
        ii. FOLFIRI (irinotecan, folinic acid [leucovorin], and 5-fluorouracil [5-FU]); **AND**
    E. Cyramza is prescribed by or in consultation with an oncologist.

    Dosing. Approve up to 8 mg/kg as an intravenous infusion administered no more frequently than once every 2 weeks.

2. **Gastric, Esophagogastric Junction, or Esophageal Cancer**. Approve if the patient meets ALL of the following (A, B, C, **AND** D):
    A. Patient is ≥ 18 years of age; **AND**
    B. Patient meets ONE of the following criteria (i, ii, **OR** iii):
        i. Cyramza will be used alone; **OR**
        ii. Cyramza will be used in combination with paclitaxel; **OR**
        iii. Cyramza will be used in combination with irinotecan; **AND**
    C. Patient has received chemotherapy with at least ONE of the following (i **OR** ii):
        i. 5-Fluorouracil (5-FU) or capecitabine; **OR**
        ii. Cisplatin, carboplatin, or oxaliplatin; **AND**
    D. Cyramza is prescribed by or in consultation with an oncologist.

    Dosing. Approve up to 8 mg/kg as an intravenous infusion administered no more frequently than once every 2 weeks.

3. **Hepatocellular Carcinoma.** Approve if the patient meets ALL of the following (A, B, C, D, **AND** E):
    A. Patient is ≥ 18 years of age; **AND**
    B. Cyramza will be used as subsequent therapy; **AND**
    C. Cyramza will be used as a single agent; **AND**
    D. Patient has an alpha fetoprotein of ≥ 400 ng/mL; **AND**
    E. Cyramza is prescribed by or in consultation with an oncologist.

    Dosing. Approve up to 8 mg/kg as an intravenous infusion administered no more frequently than once every 14 days.

4. **Non-Small Cell Lung Cancer**. Approve if the patient meets ALL of the following (A, B, **AND** C):
    A. Patient is ≥ 18 years of age; **AND**
    B. Patient meets ONE of the following criteria (i **OR** ii):
        i. Cyramza will be used as first-line or continuation therapy and the patient meets BOTH of the following (a **AND** b):

a. Patient has epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R mutation positive disease; **AND**
b. Cyramza will be used in combination with erlotinib; **OR**

ii. Cyramza will be used as subsequent therapy and the patient meets BOTH of the following (a **AND** b):
a. Cyramza will be used in combination with docetaxel intravenous infusion; **AND**
b. Patient has received targeted drug therapy if the patient's tumor is positive for a targetable mutation; **AND**
Note: Examples of targetable mutations includes sensitizing epidermal growth factor receptor mutation and anaplastic lymphoma kinase fusions.

C. Cyramza is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 10 mg/kg as an intravenous infusion no more frequently than once every 3 weeks.

Renewal Criteria

Coverage for Cyramza (ramucirumab) may be **renewed** when the following criteria are met:

A. Disease response; **AND**
B. Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: hemorrhage, arterial thrombotic events, uncontrollable hypertension, infusion-related reactions, severe proteinuria (>3g/24h), gastrointestinal perforation, wound healing complications, etc.

Dosing/Administration

Indication	Dose
Colorectal Cancer, Gastric/Esophageal/ Esophagogastric Junction Cancers, Hepatocellular Carcinoma	Administer 8 mg/kg intravenously every 14 days until disease progression or unacceptable toxicity
Non-Small Cell Lung Cancer	In combination with docetaxel: Administer 10 mg/kg intravenously every 21 days until disease progression or unacceptable toxicity In combination with erlotinib: Administer 10 mg/kg intravenously every 14 days until disease progression or unacceptable toxicity

Applicable Procedure Codes

Code	Description
J9308	Injection, ramucirumab, 5 mg

Applicable NDCs

Code	Description
00002-7669-01	Cyramza 100mg/10mL, 1 vial, single-dose in 1 carton, 10 mL in 1 vial, single-dose
00002-7678-01	Cyramza 500mg/50mL. 1 vial, single-dose in 1 carton, 50 mL in 1 vial, single-dose

ICD-10 Diagnoses

Code	Description
C15.3	Malignant neoplasm of upper third of esophagus
C15.4	Malignant neoplasm of middle third of esophagus

C15.5	Malignant neoplasm of lower third of esophagus
C15.8	Malignant neoplasm of overlapping sites of esophagus
C15.9	Malignant neoplasm of esophagus, unspecified
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C17.0	Malignant neoplasm duodenum
C17.1	Malignant neoplasm jejunum
C17.2	Malignant neoplasm ileum
C17.8	Malignant neoplasm of overlapping sites of small intestines
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of large intestines
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung

C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C78.00	Secondary malignant neoplasm of lung
C78.01	Secondary malignant neoplasm of lung
C78.02	Secondary malignant neoplasm of lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
D37.1	Neoplasm of uncertain behavior of stomach
D37.8	Neoplasm of uncertain behavior of other specified digestive organs
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.01	Personal history of malignant neoplasm of esophagus
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.038	Personal history of malignant neoplasm of large intestine
Z85.118	Personal history of other malignant neoplasm of bronchus and lung

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	3/26/2025	Annual Review: Hepatocellular Carcinoma: Removed requirements that the patient has been treated with Nexavar (sorafenib tablet) and patient has Child-Pugh Class A disease. Added requirement that Cyramza will be used as subsequent therapy. Added dosing under initial criteria Removed limitations/exclusions
EmblemHealth & ConnectiCare	3/20/2024	Annual Review: Removed PI link, added dosing chart, no criteria changes
EmblemHealth & ConnectiCare	7/18/2023	Annual Review: Gastric, Esophageal and Gastro-esophageal Junction Cancers, initiation: Initial Criteria: Added" OR used in combination with irinotecan;" Non-small cell lung cancer, initiation: Initial Criteria: Added " Patient meets of the following criteria (i or ii): i. Cyramza will be used as first-line therapy; AND a) Patient has epidermal growth factor receptor (EGFR) exon 19 deletion or L858R mutation positive disease; AND b) Cyramza will be used in combination with erlotinib; OR ii. Cyramza will be used as subsequent therapy; AND a) Cyramza will be used in combination with docetaxel intravenous infusion; AND b) Patient has received targeted drug therapy if the patient's tumor is positive for a targetable mutation Note: Examples of targetable mutations include sensitizing epidermal growth factor receptor mutation, anaplastic lymphoma kinase fusions" Removed " Patient's disease is metastatic; AND In combination with erlotinib, for the first-line treatment of patients whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations; OR

		Used as subsequent therapy following progression on or after platinum-based chemotherapy; AND Cyramza must be used in combination with docetaxel; AND Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Cyramza" Colorectal cancer, initiation: Initial Criteria Added " **OR** irinotecan" Hepatocellular carcinoma: Initial Criteria Added "Patient has Child-Pugh Class A disease; AND"
EmblemHealth & ConnectiCare	4/11/2022	Transferred policy to new template
EmblemHealth & ConnectiCare	06/17/2020	Added Criteria for NSCLC indication: In combination with erlotinib, for the first-line treatment of patients whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations
EmblemHealth & ConnectiCare	11/11/2019	Added indication for Hepatocellular carcinoma; removed hepatocellular carcinoma from limitations/exclusions

References

1. Product Information: CYRAMZA® intravenous injection, ramucirumab intravenous injection. Eli LIlly and Company (per manufacturer), Indianapolis, IN, 2019.