Clinical Policy: Ramucirumab (Cyramza)

Reference Number: CP.PHAR.119
Effective Date: 06.01.15
Last Review Date: 02.26
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Ramucirumab (Cyramza®) is a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist.

FDA Approved Indication(s)

Cyramza is indicated:

- As a single agent or in combination with paclitaxel, for treatment of adults with advanced or metastatic gastric or gastro-esophageal junction (i.e., esophagogastric junction; EGJ) adenocarcinoma, with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.
- In combination with erlotinib, for first-line treatment of adults with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations.
- In combination with docetaxel, for treatment of adults with metastatic NSCLC 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 (irinotecan, folinic acid, and 5-fluorouracil), for the treatment of adults with metastatic colorectal cancer (CRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
- As a single agent, for the treatment of adults with hepatocellular carcinoma (HCC) in patients who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL and have been treated with sorafenib.

Policy/Criteria

Provider must submit documentation (including such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Cyramza is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Esophageal, Esophagogastric Junction, and Gastric Cancer (must meet all):

1. Diagnosis of esophageal, EGJ or gastric cancer;
2. Disease is unresectable, locally advanced, recurrent, or metastatic;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;

5. Prescribed as subsequent therapy in one of the following ways (a, b, or c)*:
   a. As a single agent;
   b. In combination with paclitaxel;
   c. In combination with irinotecan with or without fluorouracil;

   **Prior authorization may be required for paclitaxel, fluorouracil, or irinotecan.*
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 8 mg per kg every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/ HIM – 12 months
Commercial – 6 months or duration of request, whichever is less

B. Non-Small Cell Lung Cancer (must meet all)**:**
1. Diagnosis of metastatic, recurrent, or advanced NSCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Request meets one of the following (a or b):*
   a. Prescribed as subsequent therapy in combination with docetaxel;
   b. Prescribed in combination with erlotinib (Tarceva®);

   **Prior authorization may be required for docetaxel or erlotinib*
5. If prescribed in combination with erlotinib, disease is positive for a sensitizing EGFR mutation (e.g., EGFR exon 19 deletions or exon 21 [L858R] substitution mutation);
6. Request meets one of the following (a, b, or c):*
   a. In combination with docetaxel: Dose does not exceed 10 mg/kg on day 1 of a 21-day cycle;
   b. In combination with erlotinib: Dose does not exceed 10 mg/kg on day 1 every 2 weeks;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/ HIM – 12 months
Commercial – 6 months or duration of request, whichever is less

C. Colorectal Cancer (must meet all):
1. Diagnosis of advanced or metastatic CRC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in combination with irinotecan or FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil);*

   **Prior authorization may be required for irinotecan or FOLFIRI.*
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 8 mg/kg every 2 weeks;

b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/ HIM – 12 months
Commercial – 6 months or duration of request, whichever is less

D. Hepatocellular Carcinoma (must meet all):

1. Diagnosis of HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. AFP ≥ 400 ng/mL;
5. Prescribed as subsequent therapy;
6. Prescribed as single-agent therapy;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 8 mg/kg every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/ HIM – 12 months
Commercial – 6 months or duration of request, whichever is less

E. Additional NCCN Recommended Uses (off-label) (must meet all):

1. Diagnosis of one of the following (a or b);
   a. Mesothelioma, classified as one of the following (i, ii, or iii):
      i. Pleural;
      ii. Pericardial;
      iii. Tunica vaginalis testis;
   b. Thymic carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. For mesothelioma, both of the following (a and b):
   a. Prescribed as subsequent therapy;
   b. Prescribed in combination with gemcitabine;*

   **Gemcitabine may require prior authorization*
5. For thymic carcinoma: Prescribed in combination with carboplatin and paclitaxel;
6. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).**

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/ HIM – 12 months
Commercial – 6 months or duration of request, whichever is less

F. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all):

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Cyramza for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, b, c, or d)*:
   a. Esophageal/EGJ/gastric cancer, CRC, HCC: New dose does not exceed 8 mg/kg every 2 weeks;
   b. NSCLC in combination with docetaxel: New dose does not exceed 10 mg/kg on day 1 of a 21-day cycle;
   c. NSCLC in combination with erlotnib: New dose does not exceed 10 mg/kg every 2 weeks;
   d. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/ HIM – 12 months
Commercial – 6 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2):

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AFP: alpha fetoprotein
CRC: colorectal carcinoma
EGJ: esophagogastric junction
EGFR: epidermal growth factor receptor
FDA: Food and Drug Administration
HCC: hepatocellular carcinoma
FOLFIRI: fluorouracil, leucovorin, irinotecan
NCCN: National Comprehensive Cancer Network
NSCLC: non-small cell lung cancer
VEGFR2: vascular endothelial growth factor receptor 2

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
HCC		
Examples of first-line therapies: Tecentriq® (atezolizumab) + bevacizumab, Imjudo® (tremelimumab-actl) + Imfinzi® (durvalumab), sorafenib, Lenvima® (lenvatinib), Tevimbra® (tislelizumab-jsgr)	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

None reported

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Gastric or EGJ adenocarcinoma	8 mg/kg IV every 2 weeks as a single agent or in combination with weekly paclitaxel	8 mg/kg
NSCLC	10 mg/kg IV on day 1 of a 21-day cycle prior to docetaxel 10 mg/kg IV every 2 weeks with daily erlotinib	10 mg/kg
CRC	8 mg/kg IV every 2 weeks prior to FOLFIRI	8 mg/kg
HCC	8 mg/kg IV every 2 weeks	8 mg/kg

VI. Product Availability

Single-dose vial: 100 mg/10 mL (10 mg/mL) solution, 500mg/50mL (10mg/mL) solution

VII. References

1. Cyramza Prescribing Information. Indianapolis, IN: Eli Lilly and Company; August 2025. Available at http://uspl.lilly.com/cyramza/cyramza.html. Accessed October 21, 2025.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at nccn.org. Accessed November 30, 2025.
3. National Comprehensive Cancer Network Guidelines. Esophageal and Esophagogastric Junction Cancers Version 4.2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed November 30, 2025.
4. National Comprehensive Cancer Network Guidelines. Gastric Cancer Version 4.2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed November 30, 2025.
5. National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer Version 1.2026. Available at https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed November 30, 2025.
6. National Comprehensive Cancer Network Guidelines. Colon Cancer Version 5.2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed November 30, 2025.
7. National Comprehensive Cancer Network Guidelines. Rectal Cancer Version 4.2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed November 30, 2025.
8. National Comprehensive Cancer Network Guidelines. Hepatocellular carcinoma Version 2.2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf. Accessed November 30, 2025.
9. National Comprehensive Cancer Network Guidelines. Mesothelioma: Pleural Version 2.2026. Available at https://www.nccn.org/professionals/physician_gls/pdf/meso_pleural.pdf. Accessed November 30, 2025.
10. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019: 20:282-96.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9308	Injection, ramucirumab, 5mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2022 annual review: revised criteria for advanced esophageal, EGJ or gastric cancer allowing combination with irinotecan with or without fluorouracil and added requirement for unresectable, locally advanced, recurrent, or metastatic disease per NCCN; updated Appendix B Therapeutic Alternatives; references reviewed and updated.	09.15.21	02.22
Template changes applied to other diagnoses/indications.	09.30.22	
1Q 2023 annual review: for esophageal, EGJ and gastric cancers, removed the requirement for "advanced" to limit possible confusion as specific disease qualifiers are outlinhed in the next criterion; Per NCCN Compendium, added requirements for confirmation of Child-Pugh class A status for HCC and use as single-agent therapy; for HCC, removed "progressive" cancer requirement as there is already a requirement for progression on or after sorafenib; updated Appendix B therapies; references reviewed and updated.	10.24.22	02.23
1Q 2024 annual review: per NCCN added off-label indication criteria for mesothelioma; references reviewed and updated.	11.05.23	02.24
1Q 2025 annual review: for colorectal cancer, added criteria for off label use in appendiceal adenocarcinoma as second-line or subsequent therapy; for HCC, removed confirmation of Child-Pugh class A status per NCCN; revised Appendix B to list only redirections; references reviewed and updated.	10.24.24	02.25
RT4: clarified FDA-Approved Indications section to specify use in adults per updated FDA labeling	04.23.25	
1Q 2026 annual review: for HCC, revised progression on sorafenib to subsequent therapy use per NCCN; removed appendiceal adenocarcinoma indication and added thymic carcinoma as off-label indication per NCCN; revised approval durations for Medicaid/ HIM to 12 months and for Commercial line of business to "6 months or duration of request, whichever is less"; references reviewed and updated.	10.21.25	02.26

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.