Clinical Policy: Ramucirumab (Cyramza)

Reference Number: CP. PHAR.119
Effective Date: 06.01.15
Last Review Date: 02.20
Line of Business: Medicaid, Commercial, HIM

Coding Implications
Revision Log

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

Description

Ramucirumab (Cyramza®) is an anti-vascular endothelial growth factor antibody.

FDA Approved Indication(s)

Cyramza is indicated:

- As a single agent or in combination with paclitaxel, for treatment of 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 the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.
- In combination with docetaxel, for treatment of metastatic non-small cell lung cancer (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 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 hepatocellular carcinoma (HCC) in patients who have an alpha fetoprotein 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 advanced esophageal, EGJ or gastric cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as subsequent therapy either as a single agent or in combination with paclitaxel;
5. 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: 6 months

B. Non-Small Cell Lung Cancer (must meet all)**:**

1. Diagnosis of recurrent, advanced, or metastatic 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 Tarceva®;
5. If prescribed in combination with Tarceva: 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 per kg on day 1 of a 21-day cycle;
   b. In combination with Tarceva: Dose does not exceed 10 mg per kg 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: 6 months

C. Colorectal Cancer (must meet all):

1. Diagnosis of metastatic CRC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as subsequent therapy in combination with irinotecan or FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil);
5. 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: 6 months

D. Hepatocellular Carcinoma (must meet all):

1. Diagnosis of HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. α-fetoprotein (AFP) ≥ 400 ng/mL;
5. Disease has progressed on or after therapy with Nexavar®;
   **Prior authorization is required for Nexavar*
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: 6 months

E. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 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 per kg every 2 weeks;
   b. NSCLC in combination with docetaxel: New dose does not exceed 10 mg per kg on day 1 of a 21-day cycle;
   c. NSCLC in combination with Tarceva: New dose does not exceed 10 mg per 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: 12 months

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 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.PHAR.21 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: α-fetoprotein
CRC: colorectal carcinoma
EGFR: epidermal growth factor receptor
EGJ: esophagogastric junction
FDA: Food and Drug Administration
HCC: Hepatocellular Carcinoma
FOLFIRI: fluorouracil, leucovorin, irinotecan
NSCLC: non-small cell lung cancer

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 and may require prior authorization.

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
paclitaxel	Esophageal, EGF, or gastric cancer: Varies	Varies
docetaxel (Taxotere®)	NSCLC: Varies	Varies
irinotecan (Camptosar®)	CRC: Varies	Varies
FOLFIRI (5-FU, leucovorin, irinotecan)	CRC: Varies	Varies
Nexavar® (sorafenib)	HCC: 400 mg PO BID	800 mg / day

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

Appendix D: General Information

- Hepatocellular carcinoma: Serum levels of alpha-fetoprotein (AFP) are typically higher for advanced HCC compared to early HCC, but overall, levels do not correlate well with clinical features of HCC, such as tumor size or vascular invasion. Not all tumors secrete AFP. The biomarker at concentrations higher than 400 ng/mL is associated with poor prognosis. After treatment with sorafenib, half the patients express alpha-fetoprotein concentrations greater than 400 ng/mL. In the pivotal trial (REACH-2), both Cyramza and placebo groups had baseline alpha-fetoprotein labs greater than 400 ng/mL. While there is debate regarding sensitivity and specificity of this biomarker, the criteria for AFP ≥ 400 ng/mL is consistent with both FDA-approved labeling and NCCN guideline recommendations.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Gastric or EGJ adenocarcinoma, HCC	8 mg/kg IV every 2 weeks	8 mg/kg
NSCLC	10 mg/kg IV on day 1 of a 21-day cycle prior to docetaxel	10 mg/kg

Indication	Dosing Regimen	Maximum Dose
	10 mg/kg IV every 2 weeks with daily erlotinib	
CRC	8 mg/kg IV every 2 weeks prior to FOLFIRI	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; June 2020. Available at http://uspl.lilly.com/cyramza/cyramza.html. Accessed June 25, 2020.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at nccn.org. Accessed June 26, 2020.
3. Esophageal and esophagogastric junction cancers (Version 2.2019). National Comprehensive Cancer Network Guidelines. Available at nccn.org. Accessed October 31, 2019.
4. Gastric cancer (Version 2.2019). National Comprehensive Cancer Network Guidelines. Available at nccn.org. Accessed October 31, 2019.
5. Non-small cell lung cancer (Version 6.2020). National Comprehensive Cancer Network Guidelines. Available at nccn.org. Accessed June 26, 2020.
6. Colon cancer (Version 3.2019). National Comprehensive Cancer Network Guidelines. Available at nccn.org. Accessed October 31, 2019.
7. Rectal cancer (Version 3.2019). National Comprehensive Cancer Network Guidelines. Available at nccn.org. Accessed October 31, 2019.
8. National Comprehensive Cancer Network. Hepatobiliary Cancers Version 3.2019. Available at www.nccn.org. Accessed October 31, 2019.
9. 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
Policy developed.	05.01.15	05.15
Policy converted to new template. Gastric cancer: removed requirement of failing a fluoropyrimidine- or platinum-containing chemotherapy; edited to allow approval if disease progress on/after prior chemotherapy per NCCN.	04.01.16	05.16

Reviews, Revisions, and Approvals	Date	P&T Approval Date
NSCLC: removed requirement of failure of platinum-based chemotherapy, simplified language to include appropriate treatment regarding ALK and EGFR aberration status. Colorectal cancer: changed requirement for the use of bevacizumab, oxaliplatin, and a fluoropyrimidine to a prior regimen containing bevacizumab per NCCN. Changed requirement of concurrent use with FOLFIRI to irinotecan containing regimen instead per NCCN; changed initial approval duration to 3 months; added impaired wound healing to reasons to discontinue per PI boxed warning.		
Esophageal cancer added to section A. Lung cancer notations of specific required prior therapy are removed. Colorectal cancer indications updated around FDA and NCCN uses. Safety criteria removed as there are no contraindications or black box warnings precluding treatment. Changed initial approval duration to 6 months. Changed continued approval to 12 months.	03.01.17	04.17
1Q18 annual review: - Age, dosing, specialist added. - NCCN recommendations removed for lung and colon cancer. - References reviewed and updated.	12.01.17	02.18
1Q 2019 annual review; HIM-Medical Benefit line of business added; NCCN and FDA-approved uses summarized for improved clarity - progression on specific therapies removed across indications; for CRC combination therapy with irinotecan is added; references reviewed and updated.	11.13.18	02.19
RT4: Criteria added for new FDA indication as a single-agent therapy for the treatment of advanced HCC; removed BBW based on updated prescribing information; references reviewed and updated.	07.05.19	
1Q 2020 annual review: no significant changes; references reviewed and updated.	10.31.19	02.20
RT4: Added criteria for new FDA indication of NSCLC in combination with Tarceva; revised HIM-medical benefit to HIM line of business; commercial line of business added; references reviewed and updated.	06.26.20	

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.