Clinical Policy: Ramucirumab (Cyramza)

Reference Number: ERX.SPA.306
Effective Date: 03.01.19
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

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 (VEGF) antibody.

FDA Approved Indication(s)
Cyramza is indicated:

- As a single agent or in combination with paclitaxel, for treatment of advanced 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 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 (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 (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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 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.*
5. Disease is unresectable, locally advanced, recurrent, or metastatic;
6. 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: 6 months

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: 6 months

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);
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: 6 months

D. Hepatocellular Carcinoma (must meet all)**:**
1. Diagnosis of progressive HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. 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/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 ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, 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 erlotinib: 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: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

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

Appendix B: Therapeutic Alternatives

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
paclitaxel, irinotecan, 5-FU	Esophageal, EGF, or gastric cancer: Varies	Varies
docetaxel (Taxotere®)	NSCLC: Varies	Varies
erlotinib (Tarceva®)	NSCLC: 150 mg PO QD	150 mg/day
irinotecan (Camptosar®), 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

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

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
HCC	8 mg/kg IV every 2 weeks	8 mg/kg

VI. Product Availability

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

VII. References

1. Cyramza Prescribing Information. Indianapolis, IN: Eli Lilly and Company; June 2021. Available at http://uspl.lilly.com/cyramza/cyramza.html. Accessed September 14, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at nccn.org. Accessed September 14, 2021.
3. National Comprehensive Cancer Network Guidelines. Esophageal and Esophagogastric Junction Cancers Version 4.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed September 14, 2021.
4. National Comprehensive Cancer Network Guidelines. Gastric Cancer Version 4.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed September 14, 2021.
5. National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer Version 5.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf . Accessed September 14, 2021.
6. National Comprehensive Cancer Network Guidelines. Colon Cancer Version 3.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf . Accessed September 14, 2021.
7. National Comprehensive Cancer Network Guidelines. Rectal Cancer Version 2.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed September 14, 2021.
8. National Comprehensive Cancer Network Guidelines. Hepatobiliary Cancers Version 4.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed September 14, 2021.
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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	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
4Q 2020 annual review: added new indication NSCLC with EGFR mutations; added criteria for NSCLC for use in combo with Erlotinib; added criteria for advanced esophageal, EGJ or gastric cancer allowing combination with fluorouracil and irinotecan per NCCN; added disease characteristics criteria for all indications per NCCN; updated Appendix B; references reviewed and updated.	10.20.20	08.20
1Q 2021 annual review: NSCLC - EGFR mutation requirement added if therapy in combination with erlotinib; CRC - subsequent therapy removed to accommodate NCCN uses; references reviewed and updated.	10.14.20	02.21
1Q 2022 annual review: revised criteria for advanced esophageal, EGJ or gastric cancer allowing combination with irinotecan with or without fluorouracil per NCCN; updated Appendix B Therapeutic Alternatives; references reviewed and updated.	09.15.21	02.22

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.