Clinical Policy Title:	ramucirumab
Policy Number:	RxA.83
Drug(s) Applied:	Cyramza®
Original Policy Date:	02/07/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

Ramucirumab (Cyramza®) is an anti-vascular endothelial growth factor antibody.
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 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 erlotinib, for the first-line treatment of patients with metastatic nonsmall cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.
- 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
ramucirumab (Cyramza®)	Gastric or EGJ adenocarcinoma	8 mg/kg every 2 weeks administered as an intravenous infusion over 60 minutes.	8 mg/kg
	NSCLC	10 mg/kg administered by intravenous infusion over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion. or 10 mg/kg IV every 2 weeks with daily erlotinib	10 mg/kg
	CRC	8 mg/kg every 2 weeks administered by intravenous infusion over 60 minutes prior to FOLFIRI administration.	8 mg/kg
	HCC	8 mg/kg every 2 weeks administered as an	8 mg/kg

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
		intravenous infusion over 60 minutes.	

Dosage Forms

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

Clinical Policy

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

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).*

Approval duration
Commercial: 6 months
Medicaid: 6 months

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

1. Diagnosis of 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 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 or b):
   a. Dose does not exceed 10 mg per kg on day 1 of a 21-day cycle;
   b. In combination with erlotinib: 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).*

Approval Duration
Commercial: 6 months
Medicaid: 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).*

Approval duration
Commercial: 6 months
Medicaid: 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)*.

Approval duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all)**:**
1. Member is currently receiving medication that has been authorized by RxAdvance or member has met initial approval criteria for the covered indications 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, or c):
   a. Esophageal/EGJ/gastric cancer, CRC, HCC: new dose not exceed 8 mg per kg every 2 weeks;
   b. NSCLC: new dose does not exceed 10 mg per kg on day 1 of a 21-day cycle;
   c. NSCLC in combination with erlotinib: 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).*

Approval duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

AFP: α-fetoprotein
CRC: colorectal carcinoma
EGJ: esophagogastric junction
FDA: Food and Drug Administration
HCC: Hepatocellular Carcinoma
FOLFIRI: fluorouracil, leucovorin, irinotecan
NSCLC: non-small cell lung cancer
EGFR: epidermal growth factor receptor

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

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

- Contraindication(s):
  - None reported

- Boxed Warning(s):
  - 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.

References

1. Cyramza Prescribing Information. Indianapolis, IN: Eli Lilly and Company; June 2020. Available at http://uspl.lilly.com/cyramza/cyramza.html. Accessed February 02, 2021.
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Guidelines. Available at https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf . Accessed February 02. 2021.
4. Gastric cancer (Version 4.2020). National Comprehensive Cancer Network Guidelines. Available at https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf . Accessed February 02, 2021.
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7. Rectal cancer (Version 1.2021). National Comprehensive Cancer Network Guidelines. Available at https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed February 02, 2021.
8. National Comprehensive Cancer Network. Hepatobiliary Cancers Version 5.2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed February 02, 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.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy was established	01/2020	02/07/2020
Policy was reviewed: 1. Clinical policy title was updated. 2. Background and Dosing information was updated with information of new FDA indication of NSCLC in combination with erlotinib". 3. Medicaid & Commercial was added in both Initial and Continued therapy approval duration. 4. Initial approval criteria I.B was added with 4th ,5th & 6th b point, new criteria for new FDA indication of NSCLC in combination with erlotinib. 5. Continued therapy criteria II.A.1 was rephrased to "Member is currently receiving medication..." and 3c point was added. 6. Appendix A was updated: added EGFR. 7. References were reviewed and updated.	02/02/2021	03/09/2021