Clinical Policy: Ramucirumab (Cyramza)

Reference Number: PA.CP.PHAR.119
Effective Date: 01/2018
Last Review Date: 01/2024

Coding Implications
Revision Log

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 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 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 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 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
It is the policy of PA Health & Wellness 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 (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).

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).*

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);*

   **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 two 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: 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. Prescribed as single-agent therapy;
7. Confirmation of Child-Pugh class A status;
8. 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: 6 months

E. Mesothelioma (off-label) (must meet all):
1. Diagnosis of mesothelioma classified as one of the following:
   a. Pleural;
   b. Pericardial;
   c. Tunica vaginalis testis;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in combination with gemcitabine;*
   **Gemcitabine may require prior authorization*
5. Prescribed as subsequent therapy;
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).*

Approval duration: 6 months

F. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

A. All Indications Listed in Section I (must meet all)**:**
1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
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).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to PA.CP.PMN.53

III. 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
VEGF: vascular endothelial growth factor

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
docetaxel, 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) FOLFOX (5-FU, leucovorin, oxaliplatin), CAPEOX (capecitabine, oxaliplatin)	CRC: Varies	Varies
Nexavar (sorafenib)	HCC: 400 mg PO BID	800 mg/day
cisplatin + pemetrexed ± bevacizumab, Opdivo® (nivolumab)/Yervoy® (ipilimumab), cisplatin + gemcitabine	Mesothelioma: 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.

IV. 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

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

VI. References

1. Cyramza Prescribing Information. Indianapolis, IN: Eli Lilly and Company; March 2022. Available at http://uspl.lilly.com/cyramza/cyramza.html. Accessed September 26.2023.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at nccn.org. Accessed November 5, 2023.
3. National Comprehensive Cancer Network Guidelines. Esophageal and Esophagogastric Junction Cancers Version 3.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf . Accessed November 5, 2023.
4. National Comprehensive Cancer Network Guidelines. Gastric Cancer Version 2.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf . Accessed November 5, 2023.
5. National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer Version 4.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf . Accessed November 5, 2023.
6. National Comprehensive Cancer Network Guidelines. Colon Cancer Version 3.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf . Accessed November 5, 2023.
7. National Comprehensive Cancer Network Guidelines. Hepatocellular Carcinoma Version 2.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed November 5, 2023.
8. National Comprehensive Cancer Network Guidelines. Mesothelioma: Pleural Version 1.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/meso_pleural.pdf. Accessed November 5, 2023.
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
Age, dosing, specialist added. NCCN recommendations removed for lung and colon cancer. References reviewed and updated.	02/2018
1Q 2019 annual review; 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.	01/2019

Reviews, Revisions, and Approvals	Date
1Q 2020 annual review: 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.	01/2020
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.	10/2020
1Q 2021 annual review: NSCLC - EGRF mutation requirement added if therapy in combination with erlotinib; references reviewed and updated.	01/2021
1Q 2022 annual review: revised criteria for advanced esophageal, EGJ or gastric cancer to align with revisions made per Centene P&T; updated Appendix B Therapeutic Alternatives; references reviewed and updated.	01/2022
1Q 2023 annual review: for esophageal, EGJ and gastric cancers, removed the requirement for “advanced” to limit possible confusion as specific disease qualifiers are outlined 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.	01/2023
1Q 2024 annual review: per NCCN added off-label indication criteria for mesothelioma; references reviewed and updated.	01/2024