

Cyramza® (ramucirumab) (Intravenous)

Document Number: IC-0199

Last Review Date: 03/05/2024

Date of Origin: 06/24/2014

Dates Reviewed: 09/2014, 01/2015, 05/2015, 11/2015, 04/2016, 08/2016, 11/2016, 05/2017, 08/2017, 11/2017, 02/2018, 05/2018, 09/2018, 12/2018, 03/2019, 06/2019, 09/2019, 12/2019, 03/2020, 06/2020, 09/2020, 12/2020, 03/2021, 06/2021, 09/2021, 12/2021, 03/2022, 06/2022, 09/2022, 12/2022, 03/2023, 06/2023, 09/2023, 12/2023, 03/2024

I. Length of Authorization

Coverage will be provided for 6 months and may be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Cyramza 100 mg/10 mL single-dose vial: 4 vials per 14 days
- Cyramza 500 mg/50 mL single-dose vial: 2 vials per 14 days

B. Max Units (per dose and over time) [HCPCS Unit]:

Indication	Billable Units (BU)	Per unit time (days)
Gastric/Esophageal/Esophagogastric Junction Cancers, Colorectal Cancer, Appendiceal Adenocarcinoma, & HCC	180 BU	14 days
NSCLC	240 BU	14 days
MPM	240 BU	21 days

III. Initial Approval Criteria ¹

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Universal Criteria ¹

- Patient does not have uncontrolled severe hypertension; **AND**
- Patient must not have had a surgical procedure within the preceding 2 weeks or have a surgical wound that has not fully healed; **AND**

Colorectal Cancer (CRC) † ‡ ^{1,3,9-11,17,18}

- Used in combination with irinotecan or FOLFIRI (irinotecan, folinic acid/leucovorin, and fluorouracil); **AND**

- Used as initial treatment for unresectable metastatic disease after previous FOLFOX (fluorouracil, folinic acid/leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months ‡; **AND**
 - Patient has proficient mismatch repair/microsatellite-stable (pMMR/MSS) disease; **OR**
- Used as subsequent therapy for progression of advanced or metastatic disease; **AND**
 - Patient has not previously been treated with irinotecan-based therapy; **AND**
 - Patient has proficient mismatch repair/microsatellite-stable (pMMR/MSS) disease; **OR**
 - Patient has deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) disease or polymerase epsilon/delta (POLE/POLD1) mutation; **AND**
 - Patient is not eligible for or has progressed on checkpoint inhibitor immunotherapy

Appendiceal Adenocarcinoma – Colon Cancer ‡³

- Used as subsequent therapy in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) for progression of advanced or metastatic disease; **AND**
- Patient has not previously been treated with irinotecan or oxaliplatin; **AND**
 - Patient has proficient mismatch repair/microsatellite-stable (pMMR/MSS) disease; **OR**
 - Patient has deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) disease or polymerase epsilon/delta (POLE/POLD1) mutation; **AND**
 - Patient is not eligible for or has progressed on checkpoint inhibitor immunotherapy

Gastric, Esophageal, and Esophagogastric Junction Cancers † ‡ Φ^{1-3,5-7,14,15}

- Patient has adenocarcinoma histology; **AND**
- Used as subsequent therapy; **AND**
- Used as a single agent OR in combination with paclitaxel OR in combination with an irinotecan-based regimen; **AND**
 - Patient has unresectable locally advanced, recurrent, or metastatic disease; **OR**
 - Patient is not a surgical candidate

Hepatocellular Carcinoma (HCC) † ‡ Φ^{1,3,4,16}

- Used as a single agent; **AND**
- Used as subsequent therapy for progressive disease; **AND**
- Patient has an alpha-fetoprotein (AFP) level of ≥ 400 ng/mL; **AND**
- Patient has Child-Pugh Class A hepatic impairment (i.e., excludes class B and C impairments); **AND**

- Patient was previously treated with sorafenib †; **OR**
- Patient has unresectable disease and is not a transplant candidate ‡; **OR**
- Patient has liver-confined disease that is inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic disease ‡; **OR**
- Patient has metastatic disease or extensive liver tumor burden ‡

Non-Small Cell Lung Cancer (NSCLC) † ‡^{1,3,8,12,13}

- Patient has recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease without evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy; **AND**
 - Used in combination with docetaxel; **AND**
 - Used as subsequent therapy for first progression after initial systemic therapy; **AND**
 - Patient has not previously been treated with docetaxel or ramucirumab; **OR**
 - Used in combination with erlotinib for epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) substitution mutations; **AND**
 - Used as first-line therapy; **OR**
 - Used for continuation of therapy following disease progression on combination erlotinib and ramucirumab therapy for asymptomatic disease, symptomatic brain lesions, or symptomatic systemic limited progression; **AND**
 - Patient has T790M negative disease

Malignant Pleural Mesothelioma (MPM)* ‡^{3,19,20}

- Used in combination with gemcitabine as subsequent therapy

**Note: May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.*

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria^{1,3,13}

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: hemorrhage, arterial thromboembolic events, uncontrolled hypertension, infusion-related reactions, severe proteinuria (> 3g/24h), nephrotic syndrome, gastrointestinal perforations, impaired wound healing, posterior reversible encephalopathy syndrome (PRES), thyroid dysfunction, worsening of pre-existing hepatic impairment, etc.; **AND**

Non-Small Cell Lung Cancer (continuation of therapy in combination with erlotinib following disease progression):

- Refer to Section III for criteria

V. Dosage/Administration ^{1,13-15,17,18,20}

Indication	Dose
Colorectal Cancer, Appendiceal Adenocarcinoma, Gastric/Esophageal/Esophagogastric Junction Cancers, Hepatocellular Carcinoma	Administer 8 mg/kg intravenously every 14 days until disease progression or unacceptable toxicity
Non-Small Cell Lung Cancer	<u>In combination with docetaxel:</u> Administer 10 mg/kg intravenously every 21 days until disease progression or unacceptable toxicity <u>In combination with erlotinib:</u> Administer 10 mg/kg intravenously every 14 days until disease progression or unacceptable toxicity
Malignant Pleural Mesothelioma	<u>In combination with gemcitabine:</u> Administer 10 mg/kg intravenously every 21 days until tumor progression or unacceptable toxicity

VI. Billing Code/Availability Information

HCPCS Code:

- J9308 – Injection, ramucirumab, 5 mg; 1 billable unit = 5 mg

NDC(s):

- Cyramza 100 mg/10 mL solution, single-dose vial: 00002-7669-xx
- Cyramza 500 mg/50 mL solution, single-dose vial: 00002-7678-xx

VII. References

1. Cyramza [package insert]. Indianapolis, IN; Eli Lilly and Company; March 2022. Accessed January 2024.
2. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-esophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014 Jan 4; 383(9911):31-9. doi: 10.1016/S0140-6736(13)61719-5. Epub 2013 Oct 3.
3. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) for ramucirumab. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the

National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed January 2024.

4. Zhu AX, Kang YK, Yen CJ, et al. REACH-2: A randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib. *J Clin Oncol* 2018;36:4003.
5. De Vita F, Borg C, Farina G, et al. Ramucirumab and paclitaxel in patients with gastric cancer and prior trastuzumab: subgroup analysis from RAINBOW study. *Future Oncol*. 2019 Aug;15(23):2723-2731. doi: 10.2217/fon-2019-0243. Epub 2019 Jun 25.
6. Shitara K, Muro K, Shimada Y, et al. Subgroup analyses of the safety and efficacy of ramucirumab in Japanese and Western patients in RAINBOW: a randomized clinical trial in second-line treatment of gastric cancer. *Gastric Cancer*. 2016 Jul;19(3):927-38. doi: 10.1007/s10120-015-0559-z. Epub 2015 Oct 28.
7. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol*. 2014 Oct;15(11):1224-35. doi: 10.1016/S1470-2045(14)70420-6. Epub 2014 Sep 17.
8. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014 Aug 23;384(9944):665-73. doi: 10.1016/S0140-6736(14)60845-X. Epub 2014 Jun 2.
9. Yoshino T, Portnoy DC, Obermannová R, et al. Biomarker analysis beyond angiogenesis: RAS/RAF mutation status, tumour sidedness, and second-line ramucirumab efficacy in patients with metastatic colorectal carcinoma from RAISE-a global phase III study. *Ann Oncol*. 2019 Jan 1;30(1):124-131. doi: 10.1093/annonc/mdy461.
10. Obermannová R, Van Cutsem E, Yoshino T, et al. Subgroup analysis in RAISE: a randomized, double-blind phase III study of irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) plus ramucirumab or placebo in patients with metastatic colorectal carcinoma progression. *Ann Oncol*. 2016 Nov;27(11):2082-2090. Epub 2016 Aug 29.
11. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol*. 2015 May;16(5):499-508. doi: 10.1016/S1470-2045(15)70127-0. Epub 2015 Apr 12.
12. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019 Dec;20(12):1655-1669. doi: 10.1016/S1470-2045(19)30634-5. Epub 2019 Oct 4.
13. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) for Non-Small Cell Lung Cancer, Version 1.2024. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN

Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed January 2024.

14. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) for Gastric Cancer, Version 2.2023. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed January 2024.
15. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) for Esophageal and Esophagogastric Junction Cancers, Version 3.2023. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed January 2024.
16. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) for Hepatocellular Carcinoma, Version 2.2023. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed January 2024.
17. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) for Colon Cancer, Version 1.2024. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed January 2024.
18. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) for Rectal Cancer, Version 6.2023. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed January 2024.
19. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) for Mesothelioma: Pleural, Version 1.2024. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most

recent and complete version of the Compendium, go online to NCCN.org. Accessed January 2024.

20. Pinto C, Zucali PA, Pagano M, et al. Gemcitabine with or without ramucirumab as second-line treatment for malignant pleural mesothelioma (RAMES): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol.* 2021 Oct;22(10):1438-1447. doi: 10.1016/S1470-2045(21)00404-6. Epub 2021 Sep 6. PMID: 34499874.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C15.3	Malignant neoplasm of upper third of esophagus
C15.4	Malignant neoplasm of middle third of esophagus
C15.5	Malignant neoplasm of lower third of esophagus
C15.8	Malignant neoplasm of overlapping sites of esophagus
C15.9	Malignant neoplasm of esophagus, unspecified
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of large intestines
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma

ICD-10	ICD-10 Description
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C45.0	Mesothelioma of pleura
C45.2	Mesothelioma of pericardium
C45.7	Mesothelioma of other sites
C45.9	Mesothelioma, unspecified
C78.00	Secondary malignant neoplasm of lung
C78.01	Secondary malignant neoplasm of lung
C78.02	Secondary malignant neoplasm of lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
D37.1	Neoplasm of uncertain behavior of stomach
D37.8	Neoplasm of uncertain behavior of other specified digestive organs
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.01	Personal history of malignant neoplasm of esophagus
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.038	Personal history of malignant neoplasm of large intestine

ICD-10	ICD-10 Description
Z85.118	Personal history of other malignant neoplasm of bronchus and lung

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: <https://www.cms.gov/medicare-coverage-database/search.aspx>. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	Applicable State/US Territory	Contractor
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC