Cyramza® (ramucirumab)
(Intravenous)

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I. Length of Authorization

- Initial: Prior authorization validity will be provided initially for 6 months.
- Renewal: Prior authorization validity may be renewed every 6 months thereafter

II. Dosing Limits

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

Indication	Billable Units (BU)	Per unit time (days)
Gastric/Esophageal/Esophagogastric Junction/Gastroesophageal Junction Cancers, CRC, Appendiceal Adenocarcinoma, & HCC	180 BU	14 days
NSCLC	240 BU	14 days
PM, Thymic Carcinoma	240 BU	21 days

III. Initial Approval Criteria [1]

Prior authorization validity 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) ¥ † ‡ [1,3,9-11,17,18,25e,28e-30e]

- Will not be used in combination with an anti-EGFR agent (e.g., panitumumab or cetuximab); **AND**

- 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**

    - Use of ramucirumab will be restricted to patients with a contraindication or intolerance to bevacizumab or bevacizumab biosimilar product; **OR**

  - Used as subsequent therapy for progression of advanced or metastatic disease after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine, unless contraindicated; **AND**
    - Patient has not previously been treated with irinotecan-based therapy; **AND**

    - Use of ramucirumab will be restricted to patients with a contraindication or intolerance to bevacizumab or bevacizumab biosimilar product

- ¥ *Note: NCCN recommends universal MMR or MSI testing in all newly diagnosed patients. If deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype (e.g., TMB>50 mut/Mb), treatment should include checkpoint inhibitor immunotherapy if the patient is a candidate.*

Appendiceal Adenocarcinoma – Colon Cancer ¥ ‡ [3]

- Used in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan); **AND**
- Used as subsequent therapy for progression of advanced or metastatic disease after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine, unless contraindicated; **AND**
- Patient has not previously been treated with irinotecan-based therapy or with oxaliplatin; **AND**

- Use of ramucirumab will be restricted to patients with a contraindication or intolerance to bevacizumab or bevacizumab biosimilar product

- ¥ *Note: NCCN recommends universal MMR or MSI testing in all newly diagnosed patients. If deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype (e.g., TMB>50 mut/Mb), treatment should include checkpoint inhibitor immunotherapy if the patient is a candidate.*

Gastric, Esophageal, and Esophagogastric/Gastroesophageal Junction Cancers † ‡ Φ [1-3,5-7,14,15,17,2e,5e]

- Patient has adenocarcinoma histology; **AND**
- Used as subsequent therapy after fluoropyrimidine- or platinum-containing chemotherapy, unless contraindicated; **AND**
- Used as a single agent OR in combination with paclitaxel OR in combination with an irinotecan-based regimen; **AND**
- Used for one of the following:

- Patient has advanced, recurrent, or metastatic disease
- Patient is not a surgical candidate; **AND**

- Single agent OR in combination with an irinotecan-based regimen:

- Patient must demonstrate an inadequate response, unless there is a contraindication or intolerance, to a generically available agent/regimen (e.g., docetaxel, paclitaxel, irinotecan, etc. [*see NCCN Esophageal and Esophagogastric Junction Cancers guidelines and Gastric Cancer guidelines for additional alternative agents/regimens*])

Hepatocellular Carcinoma (HCC) † ‡ Φ [1,3,4,16,31e-34e]

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

Non-Small Cell Lung Cancer (NSCLC) † ‡ [1,3,8,12,13,12e,13e,15e,35e,41e,51e]

- 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 platinum-based systemic therapy; **AND**
    - Patient has not previously been treated with docetaxel or ramucirumab; **AND**

      - Patients with no previous immunotherapy ONLY:

      - Use of ramucirumab will be restricted to patients with a contraindication or intolerance to pembrolizumab, nivolumab, or atezolizumab; **OR**

  - Used in combination with erlotinib; **AND**
    - Patient has epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) substitution mutation positive disease as detected by an FDA-approved or CLIA compliant test❖; **AND**
      - Used as first-line therapy; **AND**

        – Use of ramucirumab in combination with erlotinib as first-line therapy will be restricted to patients with a contraindication or intolerance to osimertinib or dacomitinib; **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

Pleural Mesothelioma (PM) ‡ [3,19,20]

- Used in combination with gemcitabine as subsequent therapy for locally advanced or metastatic disease; **AND**
- Patient has progressed during or following previous therapy with pemetrexed in combination with a platinum, unless contraindicated

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

Thymic Carcinoma ‡ [3,21,22]

- Used in combination with carboplatin and paclitaxel^; **AND**
- Used as first-line therapy for recurrent, advanced, or metastatic disease

^Ramucirumab may be continued as maintenance monotherapy

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

Enhanced Oncology Value (EOV) Program – Redacted indications
Uses not listed above have inadequate data to support efficacy and are excluded from prior authorization validity. Other treatment options including, but are not limited to, the following may be appropriate: radiation therapy, surgery, traditional chemotherapy (e.g., platinum, taxane), compassionate use/expanded access programs, clinical trials, supportive care, integrative and complementary therapies.

❖ *If confirmed using an immunotherapy assay – http://www.fda.gov/companiondiagnostics*

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

IV. Renewal Criteria [1,3,13]

Prior authorization validity 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, unless otherwise specified in section III; **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.

V. Dosage/Administration [1,13-15,17,18,20-22]

Indication	Dose
CRC, Appendiceal Adenocarcinoma, Gastric/Esophageal/ Esophagogastric/Gastroesophageal Junction Cancers, HCC	Administer 8 mg/kg intravenously every 14 days until disease progression or unacceptable toxicity
NSCLC	In combination with docetaxel: Administer 10 mg/kg intravenously every 21 days until disease progression or unacceptable toxicity In combination with erlotinib: Administer 10 mg/kg intravenously every 14 days until disease progression or unacceptable toxicity
Pleural Mesothelioma	In combination with gemcitabine: Administer 10 mg/kg intravenously every 21 days until tumor progression or unacceptable toxicity
Thymic Carcinoma	Administer 10 mg/kg intravenously every 21 days until disease 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 (STANDARD)

1. Cyramza [package insert]. Indianapolis, IN; Eli Lilly and Company; April 2025. Accessed September 2025.
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, 2025. 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 September 2025.
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 8.2025. National Comprehensive Cancer Network, 2025. 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 September 2025.
14. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) Gastric Cancer, Version 2.2025. National Comprehensive Cancer Network, 2025. 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 September 2025.
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16. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) Hepatocellular Carcinoma, Version 1.2025. National Comprehensive Cancer Network, 2025. 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 September 2025.
17. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) for Colon Cancer, Version 4.2025. National Comprehensive Cancer Network, 2025. 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 September 2025.

18. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) for Rectal Cancer, Version 2.2025. National Comprehensive Cancer Network, 2025. 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 September 2025.
19. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) for Mesothelioma: Pleural, Version 2.2025. National Comprehensive Cancer Network, 2025. 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 September 2025.
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.
21. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) for Thymomas and Thymic Carcinomas, Version 2.2025. National Comprehensive Cancer Network, 2025. 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 September 2025.
22. Proto C, Ganzinelli M, Manglaviti S, et al. Efficacy and safety of ramucirumab plus carboplatin and paclitaxel in untreated metastatic thymic carcinoma: RELEVENT phase II trial (NCT03921671). Ann Oncol 2024;35:817-826.

VIII. References (ENHANCED)

1e. Albertsson M, Johansson B, Friesland S, et al. Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent esophageal cancer. Med Oncol 2007; 24: 407-412.
2e. Ford He, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol 2014; 15: 78-86.
3e. Ajani JA, Ilson DH, Daugherty K, et al. Activity in taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 1994; 86: 1086-1091.

4e. Islon DH, Wadleigh RG, Leichman LP, et al. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol 2007; 18: 898-902.

5e. Hironaka S, Ueda S, Yasui H, aet al. Randomized, Open-Label, Phase III Study Comparing Irinotecan With Paclitaxel in Patients With Advanced Gastric Cancer Without Severe Peritoneal Metastasis After Failure of Prior Combination Chemotherapy Using Fluoropyrimidine Plus Platinum: WJOG 4007

6e. Sym, S.J., Hong, J., Park, J. et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. Cancer Chemother Pharmacol (2013) 71: 481. Trial. J Clin Oncol 2013; 31: 4438-4444.

7e. Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second line chemotherapy in gastric cancer-a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011; 47: 2306-2314.

8e. Sym SJ, Ryu MH, Lee Jl, et al. Salvage Chemotherapy With Biweekly Irinotecan, Plus 5-Fluorouracil and Leucovorin in Patients With Advanced Gastric Cancer Previously Treated With Fluoropyrimidine, Platinum, and Taxane. Am J Clin Oncol 2008;31:151-156.

9e. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015;372:2509-2520.

10e. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-413.

11e. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016; 387: 1837-1846.

12e. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017; 389:255-265.

13e. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. NEJM 2015;373:1627-1639.

14e. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. NEJM 2015;373:123-135.

15e. Horn L, Spigel DR, Vokes EE, et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). J Clin Oncol 2017; 35:3924-3933.

16e. Gettinger SN, Horn L, Gandhi L, et al. Overall survival and long-term safety of nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2015;33:2004-2012.

17e. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354-2362.

18e. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy.J Clin Oncol 2000;18:2095-2103.

19e. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-1597.

20e. Demarinis F, Paul S, Hanna N, et al. Survival update for the phase III study of pemetrexed vs. docetaxel in non-small cell lung cancer (NSCLC)

21e. Van Putten JW, Baas P, Condrington H, et al. Activity of single-agent gemcitabine as second-line treatment after previous chemotherapy or radiotherapy in advanced non-small-cell lung cancer. Lung Cancer 2001;33:289-298.

22e. Crino L, Mosconi AM, Scagliotti G, et al. Gemcitabine as second-line treatment for advanced non-small-cell lung cancer: A phase II trial. J Clin Oncol 1999;17:2081-2085.

23e. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML 18147); a randomised phase 3 trial. Lancet Oncol 2013;14:29-37.

24e. Masi G, Salvatore L, Boni L, et al. Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized BEBYP trial. Ann Oncol 2015;26:724-730.

25e. Iwamoto S, Takahashi T, Tamagawa H, et al. FOLFIRI plus bevacizumab as second-line therapy in patients with metastatic colorectal cancer after first-line bevacizumab plus oxaliplatin-based therapy: the randomized phase III EAGLE study. Ann Oncol 2015;26:1427-1433.

26e. Cartwright TH, Yim YM, Yu E, et al. Survival outcomes of bevacizumab beyond progression in metastatic colorectal cancer patients treated in US community oncology. Clin Colorectal Cancer 2012;11:238-246.

27e. Grothey A, Flick ED, Cohn AL, et al. Bevacizumab exposure beyond first disease progression in patients with metastatic colorectal cancer: analyses of the ARIES observational cohort study. Pharmacoepidemiol Drug Saf 2014;23:726-734.

28e. Van Custem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 2012;30:3499-3506.

29e. Tabernero J, Van Cutsem E, Lakomy R, et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic

colorectal cancer: prespecified subgroup analyses from the VELOUR trial. Eur J Cancer 2014;50:320-331.

30e. Goldstein DA, El-Rayes BF. Considering Efficacy and Cost, Where Does Ramucirumab Fit in the Management of Metastatic Colorectal Cancer? Oncologist 2015;20:981-982.

31e. Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015 Jul;16(7):859-70.

32e. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019 Feb;20(2):282-296.

33e. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan 7;389(10064):56-66.

34e. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 2018 Jul 5;379(1):54-63.

35e. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018 Jan 11;378(2):113-125.

36e. Hecht JR, Cohn A, Dakhil S, et al. SPIRITT: A Randomized, Multicenter, Phase II Study of Panitumumab with FOLFIRI and Bevacizumab with FOLFIRI as Second-Line Treatment in Patients with Unresectable Wild Type KRAS Metastatic Colorectal Cancer. Clin Colorectal Cancer. 2015 Jun;14(2):72-80.

37e. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol. 2008 May 10;26(14):2311-9.

38e. Peeters M, et al. Randomized Phase III Study of Panitumumab With Fluorouracil, Leucovorin, and Irinotecan (FOLFIRI) Compared With FOLFIRI Alone As Second-Line Treatment in Patients With Metastatic Colorectal Cancer. Journal of Clinical Oncology 2010 28:31, 4706-4713.

39e. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016 Apr 9;387(10027):1540-1550.

40e. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327-3334.

41e. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(11):1454-1466.

42e. Douillard JY, Ostoros G, Cobo M, et al. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. Br J Cancer. 2014;110(1):55-62.

43e. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947-957.

44e. Sakai D, Boku N, Kodera Y, et al. An intergroup phase III trial of ramucirumab plus irinotecan in third or more line beyond progression after ramucirumab for advanced gastric cancer (RINDBeRG trial). J Clin Oncol 2018;36;TPS4138.

45e. Klempner SJ, Maron SB, Chase L, Lomnicki S, Wainberg ZA, Catenacci DVT. Initial Report of Second-Line FOLFIRI in Combination with Ramucirumab in Advanced Gastroesophageal Adenocarcinomas: A Multi-Institutional Retrospective Analysis. Oncologist. 2019 Apr;24(4):475-482.

46e. van Meerbeeck JP, Baas P, Debruyne C, et al. A Phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. Cancer 1999; 85:2577.

47e. Steele JP, Shamash J, Evans MT, et al. Phase II study of vinorelbine in patients with malignant pleural mesothelioma. J Clin Oncol 2000; 18:3912.

48e. Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. Lung Cancer. 2009 Jan;63(1):94-7.

49e. Zalcman G, Mazieres J, Greillier L, et al. Second/third-line nivolumab vs nivo plus ipilimumab in malignant pleural mesothelioma: Long-term results of IFCT-1501 MAPS2 phase IIR trial with a focus on hyperprogression (HPD). Ann of Oncol 2016 Oct;30(suppl_5):v747.

50e. Disselhorst MJ, Quispel-Janssen J, Lalezari F, et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial. Lancet Respir Med. 2019 Mar;7(3):260-270.

51e. Kawashima Y, Fukuhara T, Saito H, et al. Bevacizumab plus erlotinib versus erlotinib alone in Japanese patients with advanced, metastatic, EGFR-mutant non-small-cell lung cancer (NEJ026): overall survival analysis of an open-label, randomised, multicentre, phase 3 trial. Lancet Respir Med. 2022 Jan;10(1):72-82.

52e. Kawamoto Y, Yuki S, Sawada K, et al. Phase II Study of Ramucirumab Plus Irinotecan Combination Therapy as Second-Line Treatment in Patients with Advanced Gastric Cancer: HGCSG1603. Oncologist. 2022 Aug 5;27(8):e642-e649. doi: 10.1093/oncolo/oyac086. PMID: 35579511; PMCID: PMC9355819.

53e. Prime Therapeutics Management. Cyramza Clinical Literature Review Analysis. Last updated September 2025. Accessed September 2025.

Appendix A – Non-Quantitative Treatment Limitations (NQTL) Factor Checklist

Non-quantitative treatment limitations (NQTLs) refer to the methods, guidelines, standards of evidence, or other conditions that can restrict how long or to what extent benefits are provided under a health plan. These may include things like utilization review or prior authorization. The utilization management NQTL applies comparably, and not more stringently, to mental health/substance use disorder (MH/SUD) Medical Benefit Prescription Drugs and medical/surgical (M/S) Medical Benefit Prescription Drugs. The table below lists the factors that were considered in designing and applying prior authorization to this drug/drug group, and a summary of the conclusions that Prime's assessment led to for each.

Factor	Conclusion
Indication	Yes: Consider for PA
Safety and efficacy	No: PA not a priority
Potential for misuse/abuse	No: PA not a priority
Cost of drug	Yes: Consider for PA

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

ICD-10	ICD-10 Description
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
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
C37	Malignant neoplasm of thymus
C45.0	Mesothelioma of pleura
C45.2	Mesothelioma of pericardium
C45.7	Mesothelioma of other sites

ICD-10	ICD-10 Description
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
D15.0	Benign neoplasm of thymus
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
D38.4	Neoplasm of uncertain behavior of thymus
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
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.238	Personal history of other malignant neoplasm of thymus

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)

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
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
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC