UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Oncology (Injectable) – Cyramza Utilization Management Medical Policy
- Cyramza® (ramucirumab intravenous infusion – Eli Lilly)

REVIEW DATE: 06/11/2025

OVERVIEW

Cyramza, a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist, is indicated for the following:[1]

- **Colorectal cancer**, metastatic, in combination with FOLFIRI (irinotecan, leucovorin, and 5-fluorouracil [5-FU]) for patients with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
- **Gastric** or **gastroesophageal junction adenocarcinoma**, as a single agent or in combination with paclitaxel for patients with advanced or metastatic disease with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.
- **Hepatocellular carcinoma**, as a single agent in patients who have an alpha fetoprotein of ≥ 400 ng/mL and have been treated with Nexavar® (sorafenib tablets).
- **Non-small cell lung cancer** (NSCLC), metastatic, in combination with docetaxel for disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Cyramza.
- **NSCLC**, metastatic, in combination with erlotinib for the first-line treatment of NSCLC with *EGFR* exon 19 deletions or exon 21 (L858R) mutations.

Dosing

The recommended dose of Cyramza is 8 mg/kg administered by intravenous infusion once every 2 weeks for gastric cancer, colorectal cancer, and hepatocellular cancinoma.[1] The recommended dose for NSCLC is 10 mg/kg administered by intravenous infusion no more frequently than once every 2 weeks. Cyramza is continued until disease progression or unacceptable adverse events. The dose of Cyramza is reduced, withheld, or discontinued to manage adverse events.

Guidelines

Cyramza is addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **Colon cancer** (version 3.2025 – April 24, 2025) and **Rectal cancer** (version 2.2025 – March 31, 2025): Guidelines recommend Cyramza as primary therapy and subsequent therapy for patients with unresectable advanced or metastatic disease, and as adjuvant treatment for unresectable metachronous metastases that converted to resectable disease after primary treatment, in combination with either irinotecan or FOLFIRI.[2-4]
- **Gastric cancer** (version 2.2025 – April 4, 2025) and **esophageal and esophagogastric junction cancers** (version 3.2025 – April 22, 2025): Guidelines recommend Cyramza as palliative treatment for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease.[4-6]
- **Hepatocellular carcinoma**: Guidelines (version 1.2025 – March 20, 2025) recommend Cyramza as a single agent for the treatment of patients with progressive disease with an alpha fetoprotein ≥ 400 ng/mL.[4,8]
- **NSCLC**: Guidelines (version 3.2025 – January 14, 2025) recommend Cyramza as subsequent therapy in combination with docetaxel for recurrent, advanced, or metastatic disease for patients

who have not previously received docetaxel either following progression on initial cytotoxic therapy or for further progression on a systemic immune checkpoint inhibitor or other systemic therapy.[4,7] Cyramza is also recommended in combination with erlotinib for patients with EGFR exon 19 deletion or exon 21 L858R mutation positive, recurrent, advanced, or metastatic disease as first-line therapy or as continuation therapy following disease progression on Cyramza and erlotinib.

- **Mesothelioma – Pleural**: Guidelines (version 2.2025 – January 14, 2025) recommend Cyramza as subsequent therapy in combination with gemcitabine for pleural mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.[4,9]
- **Thymomas and Thymic carcinomas**: Guidelines (version 1.2025 – October 30, 2024) recommend Cyramza as treatment for resectable, recurrent, advanced, or metastatic thymic carcinoma, used in combination with carboplatin and paclitaxel (category 2A).[11]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Cyramza. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cyramza as well as the monitoring required for adverse events and long-term efficacy, approval requires Cyramza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cyramza is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Colon, Rectal, or Appendiceal Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):

i. Patient meets ALL of the following (a, b, and c):

a) Patient has unresectable metachronous metastases; AND

b) Disease is proficient mismatch repair/microsatellite-stable (pMMR/MSS) or deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation positive with ultra-hypermutated phenotype; AND

c) Patient meets ONE of the following [(1) or (2)]:

(1) Patient has been previously treated with FOLFOX or CapeOX; OR
Note: FOLFOX includes 5-fluorouracil (5-FU), leucovorin, and oxaliplatin and CapeOX includes capecitabine and oxaliplatin

(2) The medication is used as adjuvant therapy.

ii. Patient meets ALL of the following (a, b, c, and d):

a) Patient has advanced or metastatic disease; AND

b) Disease is proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progressed on checkpoint inhibitor therapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation positive with ultra-hypermutated phenotype; AND
Note: Examples of checkpoint inhibitors include Keytruda (pembrolizumab intravenous infusion) and Opdivo (nivolumab intravenous infusion). Ultra-hypermutated phenotype is TMB > 50 mut/MB).

c) The medication is used as subsequent therapy; AND

d) Patient has not been treated with irinotecan; AND

C) The medication will be used in combination with ONE of the following (i or ii):

i. Irinotecan; OR

ii. FOLFIRI; AND
Note: FOLFIRI includes irinotecan, folinic acid [leucovorin], and 5-fluorouracil [5-FU].

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 8 mg/kg as an intravenous infusion administered no more frequently than once every 2 weeks.

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2. Gastric, Esophagogastric Junction, or Esophageal Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i, ii, or iii):

i. The medication will be used as a single agent; OR

ii. The medication will be used in combination with paclitaxel; OR

iii. The medication will be used in combination with irinotecan; AND

C) The medication is used as subsequent therapy; AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 8 mg/kg as an intravenous infusion administered no more frequently than once every 2 weeks.

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3. Hepatocellular Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) The medication will be used as subsequent therapy; AND

C) The medication will be used as a single agent; AND

D) Patient has an alpha fetoprotein of ≥ 400 ng/mL; AND

E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 8 mg/kg as an intravenous infusion administered no more frequently than once every 14 days.

Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Patient meets BOTH of the following (a and b):
    - **a)** Patient has epidermal growth factor receptor (*EGFR*) exon 19 deletion or exon 21 L858R mutation positive disease; AND
    - **b)** The medication will be used in combination with erlotinib; OR
  - **ii.** Patient meets BOTH of the following (a and b):
    - **a)** The medication will be used as subsequent therapy; AND
    - **b)** The medication will be used in combination with docetaxel; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 10 mg/kg as an intravenous infusion no more frequently than once every 3 weeks.

Other Uses with Supportive Evidence

5. Mesothelioma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has ONE of the following (i, ii, or iii):
  - **i.** Pleural mesothelioma; OR
  - **ii.** Pericardial mesothelioma; OR
  - **iii.** Tunica vaginalis testis mesothelioma; AND
- **C)** The medication is used as subsequent therapy; AND
- **D)** The medication is used in combination with gemcitabine; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 10 mg/kg as an intravenous infusion no more frequently than once every 3 weeks.

6. Thymic Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following criteria (i or ii):
  - **i.** The medication will be used with carboplatin and paclitaxel; OR
  - **ii.** The medication will be used as maintenance therapy.
- **C)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 10 mg/kg as an intravenous infusion no more frequently than once every 3 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cyramza is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Cyramza® intravenous infusion [prescribing information]. Indianapolis, IN: Eli Lilly; April 2025..

2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 3.2025 – April 24, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 14, 2025.
3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 2.2025 – March 31, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 14, 2025.
4. The NCCN Drugs & Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 14, 2025 Search term: ramucirumab.
5. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (version 2.2025 – April 4, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 14, 2025.
6. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 3.2025 – April 22, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 14, 2025.
7. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2025 – January 14, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 14, 2025.
8. The NCCN Hepatocellular Carcinoma Clinical Practice Guidelines in Oncology (version 1.2025 – March 20, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 14, 2025.
9. The NCCN Mesothelioma: Pleural Clinical Practice Guidelines in Oncology (version 2.2025 – January 14, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 14, 2025.
10. Pinto C, Zucali PA, Pagano M, et al. Gemcitabine with or without ramucirumab as second-line treatment for malignant pleural mesothelioma (RAMES): a randomized, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2021;22:1438-1447.
11. The NCCN Thymomas and Thymic Carcinomas Clinical Practice Guidelines in Oncology (version 1.2025 – October 30, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 14, 2025.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Colon, Rectal or Appendiceal Cancer:** Appendiceal was added to the condition of approval. A requirement was added that the patient is ≥ 18 years of age. A requirement was added that the patient has advanced or metastatic disease. **Gastric, Esophagogastric Junction, or Esophageal Cancer:** A requirement was added that the patient is ≥ 18 years of age. **Hepatocellular Carcinoma:** A requirement was added that the patient is ≥ 18 years of age added. **Non-Small Cell Lung Cancer:** A requirement was added that the patient is ≥ 18 years of age. "Or continuation" was added as an additional option in reference to that Cyramza will be used as first-line or continuation therapy. "Exon 21" added as a descriptor to L858R mutation such that the patient has epidermal growth factor receptor exon 19 deletion or exon 21 L858R mutation positive disease. **Mesothelioma:** Added new condition of approval.	06/14/2023
Annual Revision	**Hepatocellular Carcinoma:** Removed requirements that the patient has been treated with Nexavar (sorafenib tablet) and patient has Child-Pugh Class A disease. Added requirement that Cyramza will be used as subsequent therapy.	06/12/2024
Annual Revision	**Thymic Carcinomas:** Added new condition of approval and criteria. **Colon, Rectal, or Appendiceal Cancer:** Removed the requirement that the "patient has received oxaliplatin and fluoropyrimidine.. Added options for approval for patient with unresectable metachronous metastases, if proficient mismatch repair/microsatellite-stable (pMMR/MSS) or deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation positive with ultra-hypermutated phenotype, and if the patient has been previously treated with FOLFOX or CapeOX or the medication is used as adjuvant therapy. For advanced or metastatic disease; added a requirement that disease is (pMMR/MSS) or ineligible for or progressed on checkpoint inhibitor therapy for (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation positive with ultra-hypermutated phenotype, if the patient has not previously been treated with irinotecan, and the medication is used for subsequent therapy. **Gastric, Esophagogastric Junction, or Esophageal Cancer:** Removed the requirement that the"patient has received chemotherapy with 5-Fluorouracil (5-FU), capecitabine, cisplatin, carboplatin, or oxaliplatin. Added a requirement that "the medication is used as subsequent therapy.. **Non-Small Cell Lung Cancer:** Removed the requirement that "Cyramza will be used as first-line or continuation therapy" and that the "patient has received targeted drug therapy if the patient's tumor is positive for a targetable mutation".	06/11/2025