UTILIZATION MANAGEMENT MEDICAL POLICY

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

REVIEW DATE: 06/12/2024

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 patients with 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 3.2024 – May 24, 2024) and **rectal cancer** (version 2.2024 – April 30, 2024): 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 2.2024 – May 29, 2024) and **esophageal and esophagogastric junction cancers** (version 3.2024 – April 26, 2024): 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 1.2024 – April 9, 2024) 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 5.2024 – April 23, 2024) 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 1.2024 – November 21, 2023) recommend Cyramza as subsequent therapy in combination with gemcitabine for pleural mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.[4,9]

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, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient had advanced or metastatic disease; AND
   - **C)** Patient has received BOTH of the following (i and ii):
     - **i.** Oxaliplatin; AND
     - **ii.** Fluoropyrimidine (e.g., 5-fluorouracil [5-FU], capecitabine); AND
   - **D)** Cyramza will be used in combination with ONE of the following (i or ii):
     - **i.** Irinotecan; OR
     - **ii.** FOLFIRI (irinotecan, folinic acid [leucovorin], and 5-fluorouracil [5-FU]); AND
   - **E)** Cyramza 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.

---

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 criteria (i, ii, or iii):
  i. Cyramza will be used alone; OR
  ii. Cyramza will be used in combination with paclitaxel; OR
  iii. Cyramza will be used in combination with irinotecan; AND
C) Patient has received chemotherapy with at least ONE of the following (i or ii):
  i. 5-Fluorouracil (5-FU) or capecitabine; OR
  ii. Cisplatin, carboplatin, or oxaliplatin; AND
D) Cyramza 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.

---

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) Cyramza will be used as subsequent therapy; AND
C) Cyramza will be used as a single agent; AND
D) Patient has an alpha fetoprotein of ≥ 400 ng/mL; AND
E) Cyramza 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.

---

4. 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. Cyramza will be used as first-line or continuation therapy and the 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) Cyramza will be used in combination with erlotinib; OR
  ii. Cyramza will be used as subsequent therapy and the patient meets BOTH of the following (a and b):
    a) Cyramza will be used in combination with docetaxel intravenous infusion; AND
    b) Patient has received targeted drug therapy if the patient's tumor is positive for a targetable mutation; AND
    Note: Examples of targetable mutations includes sensitizing epidermal growth factor receptor mutation and anaplastic lymphoma kinase fusions.
C) Cyramza 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) Medication is used as subsequent therapy; AND
D) Medication is used in combination with gemcitabine; AND
E) 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; March 2022.
2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 3.2024 – May 24, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 4, 2024.
3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 2.2024 – April 30, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 4, 2024.
4. The NCCN Drugs & Biologics Compendium. © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 4, 2024. Search term: ramucirumab.
5. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (version 2.2024 – May 29, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 4, 2024.
6. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 3.2024 – April 26, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 4, 2024.
7. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 5.2024 – April 23, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 4, 2024.
8. The NCCN Hepatocellular Carcinoma Clinical Practice Guidelines in Oncology (version 1.2024 – April 9, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 4, 2024.
9. The NCCN Mesothelioma: Pleural Clinical Practice Guidelines in Oncology (version 1.2024 – November 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 4, 2024.
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.

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	06/14/2023

	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.	
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