POLICY: Oncology - Cyramza® (ramucirumab injection for intravenous use – Eli Lilly and Company)

DATE REVIEWED: 06/10/2020

OVERVIEW

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

1) Gastric or gastroesophageal (GE) junction adenocarcinoma, as a single agent or in combination with paclitaxel injection for the treatment of patients with advanced or metastatic disease with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy;
2) Metastatic non-small cell lung cancer (NSCLC), in combination with docetaxel intravenous injection (Docefrez™, Taxotere®, generics) for the treatment of 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.
3) Metastatic NSCLC, in combination with erlotinib for the first-line treatment of NSCLC with EGFR exon 19 deletions or exon 21 (L858R) mutations.
4) Metastatic colorectal cancer (mCRC), in combination with FOLFIRI (irinotecan, leucovorin, and 5-fluorouracil [5-FU]) for the treatment of patients with disease progression on or after prior therapy with Avastin® (bevacizumab intravenous injection), oxaliplatin, and a fluoropyrimidine.
5) Hepatocellular carcinoma (HCC), as a single agent in patients who have an alpha fetoprotein of ≥ 400 ng/mL and have been treated with sorafenib.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on colon cancer (version 3.2020 – May 6, 2020) and rectal cancer (version 4.2020 – May 21, 2020) 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]

The NCCN guidelines on gastric cancer (version 2.2020 – May 13, 2020) and esophageal and esophagogastric junction cancers (version 2.2020 – May 13, 2020) recommend Cyramza as palliative treatment for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease.[4-6]

The NCCN guidelines on NSCLC (version 5.2020 – May 27, 2020) recommend Cyramza as subsequent therapy in combination with docetaxel for 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 mutation positive, recurrent, advanced, or metastatic disease as first-line therapy or as continuation therapy following disease progression on Cyramza and erlotinib.

The NCCN guidelines for hepatobiliary cancers (version 3.2020 – June 1, 2020) recommends Cyramza as a single agent for the treatment of patients with progressive disease with an alpha fetoprotein ≥ 400 ng/mL.[4,8]

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.

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

FDA-Approved Indications

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1. Colon or Rectal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Cyramza is prescribed by or in consultation with an oncologist; AND
- **B)** The patient has received oxaliplatin, and a fluoropyrimidine (e.g., 5-fluorouracil [5-FU], capecitabine); AND
- **C)** Cyramza will be used in combination with irinotecan or with FOLFIRI (irinotecan, folinic acid [leucovorin], and 5-fluorouracil [5-FU]).

Dosing. Approve the following dosing regimen: Each individual dose must not exceed 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 the following criteria (A, B, and C):
- **A)** Cyramza is prescribed by or in consultation with an oncologist; AND
- **B)** The 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 fluorouracil and irinotecan; AND
- **C)** The 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.

Dosing. Approve the following dosing regimen: Each individual dose must not exceed 8 mg/kg as an intravenous infusion administered no more frequently than once every 2 weeks.

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3. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Cyramza is prescribed by or in consultation with an oncologist; AND
- **B)** The patient meets one of the following criteria (i or ii):
  - **i.** Cyramza will be used as first-line therapy; AND

a) The patient has epidermal growth factor receptor (EGFR) positive disease; AND
b) Cyramza will be used in combination with erlotinib (Tarceva®, generics); OR

ii. Cyramza will be used as subsequent therapy; AND
a) Cyramza will be used in combination with docetaxel intravenous injection (Docefrez™, Taxotere®, generics); AND
b) The patient has received targeted drug therapy if the patient's tumor is positive for a targetable mutation (i.e., sensitizing epidermal growth factor receptor mutation, anaplastic lymphoma kinase fusions).

Dosing. Approve the following dosing regimen: Each individual dose must not exceed 10 mg/kg as an intravenous infusion no more frequently than once every 3 weeks.

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4. **Hepatocellular Carcinoma.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
A) Cyramza is prescribed by or in consultation with an oncologist; AND
B) The patient has been treated with Nexavar® (sorafenib tablet); AND
C) Cyramza will be used as a single agent; AND
D) The patient has an alpha fetoprotein of ≥ 400 ng/mL.

Dosing. Approve the following dosing regimen: Each individual dose must not exceed 8 mg/kg as an intravenous infusion administered no more frequently than once every 14 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cyramza has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

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® injection for intravenous use [prescribing information]. Indianapolis, IN: Eli Lilly and Company; June 2020.
2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 3.2020 – May 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 3, 2020.
3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – May 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 3, 2020.
4. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 3, 2020. Search term: ramucirumab.
5. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 - May 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 3, 2020.
6. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (Version 2.2020 – May 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 3, 2020.
7. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 5.2020 – May 27, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 3, 2020.
8. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (Version 3.2020 – June 1, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 3, 2020.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual	Criteria for NSCLC were revised.	05/17/2017
Annual	• NSCLC: Criteria were divided into non-squamous cell and squamous cell histologies. For non-squamous cell histologies, the list of targeted therapies used for each aberration was removed; testing for both EGFR and ALK is required; testing for ROS1 was removed; EGFR and ALK are negative was added as an option after testing. In Labs/Diagnostics, testing for ROS1 rearrangements was removed.	06/27/2018
Annual	Colon or rectal cancer. Changed name to Colon or Rectal Cancer. Removed advanced or metastatic colorectal cancer that has progressed on or after therapy with Avastin from 1B and added in combination with irinotecan to 1C. Gastric, Esophagogastric Junction, or Esophageal Cancer. Removed locally advanced or metastatic disease criteria from policy. Non-Small Cell Lung Cancer. Removed advanced or metastatic disease criteria from policy. Reworded criteria regarding the use of applicable targetable mutation therapies to be in line with other oncology policies. Hepatocellular carcinoma. Added approval criteria for hepatocellular carcinoma.	06/12/2019

	Approval duration. Increased approval duration to 1 year for all indications. Conditions Not Recommended For Approval. Removed breast cancer from the Conditions Not Recommended For Approval section. Removed Patient has been Started on Cyramza and Waste Management for All Indications sections.	
Annual Revision	Gastric, Esophagogastric Junction, or Esophageal Cancer: Added criteria for use of Cyramza in combination with fluorouracil and irinotecan. Non-Small Cell Lung Cancer: Added criteria for the use of Cyramza in combination with erlotinib as first-line therapy for patients with EGFR positive disease. Removed criteria for histologic subtypes of NSCLC. Removed Other Cancer Related Indications criteria.	06/10/2020

NSCLC – Non-small cell lung cancer; EGFR – Epidermal growth factor receptor; ALK – Anaplastic lymphoma kinase.