BlueCross BlueShield
Federal Employee Program.
Blue Cross Blue Shield Association
750 9th St NW, Suite 900
Washington, D.C. 20001
1-800-624-5060
Fax 1-877-378-4727

5.21.044

Section:	Prescription Drugs	**Effective Date:**	April 1, 2025
Subsection:	Antineoplastic Agents	**Original Policy Date:**	May 30, 2014
Subject:	Cyramza	**Page:**	1 of 7

Last Review Date: March 7, 2025

Cyramza

Description

Cyramza (ramucirumab)

Background
Cyramza (ramucirumab) is a single-agent treatment or combination for patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, metastatic non-small cell lung cancer (NSCLC), colorectal cancer, or hepatocellular carcinoma. Some of these tumors create proteins called vascular endothelial growth factors (VEGF). These proteins attach to the receptors of blood vessel cells causing new blood vessels to form around the tumors, enabling growth. Cyramza blocks VEGF proteins from linking to the blood vessels helping to inhibit tumor growth by slowing new blood vessel formation and the blood supply that feeds tumors (1).

Regulatory Status
FDA-approved indications: Cyramza is a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist indicated for the treatment of: (1)

1. **Gastric Cancer** - Cyramza as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic, gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine-or platinum-containing chemotherapy.
2. **Non-Small Cell Lung Cancer**
    a. Cyramza, in combination with erlotinib, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

b. Cyramza, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Cyramza.

3. **Metastatic Colorectal Cancer** - Cyramza, in combination with FOLFIRI, for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
4. **Hepatocellular Carcinoma** - Cyramza, as a single agent, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have an alpha fetoprotein (AFP) of ≥400 ng/mL and have been treated with sorafenib.

Cyramza has warnings for increased risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue Cyramza in patients who experience severe bleeding. Cyramza warnings also include gastrointestinal perforation and impaired wound healing. If either of these adverse effects occur, Cyramza should be discontinued (1).

Cyramza has an increased incidence of severe hypertension in patients receiving it. Hypertension should be controlled prior to initiating treatment. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Temporarily suspend Cyramza for severe hypertension until medically controlled. Permanently discontinue Cyramza if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy (1).

Cyramza is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue Cyramza in patients who experience a gastrointestinal perforation (1).

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported. Confirm the diagnosis of RPLS with MRI and discontinue Cyramza in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death (1).

Monitor patients during the infusion for signs and symptoms of infusion related reactions (IRR) in a setting with available resuscitation equipment. Immediately and permanently discontinue Cyramza for Grade 3 or 4 IRRs (1).

The safety and effectiveness of Cyramza in pediatric patients have not been established (1).

Related policies
Bevacizumab, Zaltrap

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Cyramza may be considered **medically necessary** if the conditions indicated below are met.

Cyramza may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Advanced or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma
    a. Used as a single agent (monotherapy) or combination therapy with paclitaxel
    b. Patient has received prior chemotherapy containing fluoropyrimidine or platinum and experienced disease progression on or after therapy
2. Metastatic non-small cell lung cancer (NSCLC) and **ONE** of the following:
    a. Used in combination with docetaxel
        i. Patient has received prior chemotherapy containing platinum and experienced disease progression on or after therapy
        ii. Positive EGFR or ALK tumor expression **only**: patient has had disease progression on FDA-approved therapy
    b. Used in combination with erlotinib

i. First-line treatment
ii. Tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations

3. Metastatic colorectal cancer
    a. Combination therapy with FOLFIRI
    b. Patient has received prior chemotherapy containing bevacizumab, oxaliplatin, and a fluoropyrimidine and experienced disease progression on or after therapy
4. Hepatocellular carcinoma (HCC)
    a. Used as a single agent (monotherapy)
    b. Alpha fetoprotein ≥(AFP) 400 ng/mL
    c. Patient has previously been treated with sorafenib

AND the following for **ALL** diagnoses:

1. Confirmation that patient does not have the following and if condition develops, therapy will be discontinued:
    a. Hemorrhage or any severe bleeding event
    b. Arterial thromboembolic events (ATEs)

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Advanced or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma
2. Metastatic non-small cell lung cancer (NSCLC)
3. Metastatic colorectal cancer
4. Hepatocellular carcinoma (HCC)

AND ALL of the following:

1. Patient has not experienced disease progression or unacceptable toxicity
2. Confirmation that patient does not have the following and if condition develops, therapy will be discontinued:

a. Hemorrhage or any severe bleeding event
b. Arterial thromboembolic events (ATEs)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Cyramza (ramucirumab) is a single-agent treatment or combination for patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, metastatic non-small cell lung cancer (NSCLC), colorectal cancer, or hepatocellular carcinoma. Some of these tumors create proteins called vascular endothelial growth factors (VEGF). These proteins attach to the receptors of blood vessel cells causing new blood vessels to form around the tumors, enabling growth. Cyramza blocks VEGF proteins from linking to the blood vessels helping to inhibit tumor growth by slowing new blood vessel formation and the blood supply that feeds tumors. The safety and effectiveness of Cyramza in patients under 18 years of age have not been established (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Cyramza while maintaining optimal therapeutic outcomes.

References

1. Cyramza [package insert]. Indianapolis, IN: Eli Lilly and Co.; March 2022.
2. NCCN Drugs & Biologics Compendium® Ramucirumab 2025. National Comprehensive Cancer Network, Inc. Accessed on January 24, 2025.

Policy History

Date	Action
May 2014	New policy addition
September 2014	Annual review
November 2014	Addition of metastatic and disease progression and allow combination therapy with paclitaxel. Removal of monitoring of IRR, Reversible Posterior Leukoencephalopathy Syndrome (RPLS), hypertension and gastrointestinal perforation.
January 2015	Addition of metastatic non-small cell lung cancer (NSCLC)
March 2015	Annual editorial review and reference update
May 2015	Addition of Metastatic Colorectal Cancer
December 2015	Annual review
March 2016	Annual editorial review Policy number change from 5.04.44
June 2016	Annual editorial review and reference update
June 2017	Annual editorial review and reference update
September 2017	Annual review
June 2018	Annual editorial review
May 2019	Addition of indication: hepatocellular carcinoma (HCC)
June 2019	Annual review
December 2019	Annual editorial review and reference update. Revised metastatic NSCLC requirement to either be negative for EGFR/ALK tumor expression or be positive and have disease progression on targeted therapy
June 2020	Annual review and reference update. Addition of indication: metastatic NSCLC in combination with erlotinib
October 2020	Revised requirement for metastatic colorectal cancer: “Patient has received prior chemotherapy containing bevacizumab, oxaliplatin, and a fluoropyrimidine and experienced disease progression on or after therapy”. Clarified language under disease progression and mutation requirements for metastatic NSCLC.
December 2020	Annual review
March 2021	Annual review and reference update
March 2022	Annual review and reference update
September 2022	Annual review and reference update
March 2023	Annual review and reference update
June 2023	Annual review and reference update
March 2024	Annual review and reference update
March 2025	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 7, 2025 and is effective on April 1, 2025.