09-J2000-14

Original Effective Date: 09/15/14

Reviewed: 09/09/26

Revised: 10/15/26

Subject: Ramucirumab (Cyramza™) Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References			

DESCRIPTION:

Ramucirumab (Cyramza), a fully human monoclonal antibody that binds with high affinity to the extracellular domain of vascular endothelial growth factor receptor 2 (VEGFR2), preventing the binding of VEGF-A, VEGF-C, and VEGF-D, was approved by the U.S. Food and Drug Administration (FDA) in April 2014 for the treatment of advanced gastric cancer or gastro-esophageal junction adenocarcinoma, as a single-agent after prior fluoropyrimidine- or platinum-containing chemotherapy. In December 2014, the FDA expanded the approved use of ramucirumab to treat patients with metastatic non-small cell lung cancer (NSCLC).

The safety and efficacy of ramucirumab were evaluated in subjects (n=355) with locally advanced or metastatic gastric cancer (including adenocarcinoma of the gastro-esophageal junction [GEJ]) who previously received platinum- or fluoropyrimidine-containing chemotherapy in multicenter, double-blind, randomized clinical trial. Patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Patients received either an intravenous infusion of ramucirumab 8 mg/kg (n=238) or placebo solution (n=117) every 2 weeks. The primary endpoint was overall survival; progression-free survival an additional outcome measure.

Efficacy results are summarized in Table 1:

Table 1

Overall Response Rate and Duration of Response		
	Ramucirumab N=238	**Placebo N=117**
Overall Survival		
Number of deaths (%)	179 (75%)	99 (85%)
Median – months (95% CI)	5.2 (4.4, 5.7)	3.8 (2.8, 4.7)
Hazard Ratio (95% CI)	0.78 (0.60, 0.998)	
Stratified Log-rank p-value	0.047	
Progression-free Survival		
Number of events (%)	199 (84%)	108 (92%)
Median – months (95% CI)	2.1 (1.5, 2.7)	1.3 (1.3, 1.4)

Hazard Ratio (95% CI)	0.48 (0.38, 0.62)
Stratified Log-rank p-value	<0.001

Ramucirumab carries a boxed warning of hemorrhage. The most frequently reported adverse event was hypertension.

National Comprehensive Cancer Network (NCCN) Guidelines for Colon Cancer (Verion 2.2021), Esophageal and Esophagogastric Junction Cancers (Version 4.2021), Gastric Cancer (Version 4.2021), Hepatobiliary Cancer (Version 4.2021), Non-Small Cell Lung Cancer (Version 5.2021), and Rectal Cancer (Version 1.2021) contain recommendations for use of ramucirumab.

POSITION STATEMENT:

Drug Waste Reduction: Additional medical necessity criteria for dose optimization may apply depending on the requested dose and member's benefit. Refer to Medical Coverage Guideline Drug Waste Reduction, 09-J5000-54.

Initiation of ramucirumab (Cyramza) **meets the definition of medical necessity** for members diagnosed with **ANY** of the following conditions when **ALL** associated criteria are met:

1. Colon cancer, including appendiceal adenocarcinoma
    a. Member's disease is advanced or metastatic
    b. Use will be in combination with either of the following:
        i. Irinotecan
        ii. FOLFIRI (fluorouracil, leucovorin, and irinotecan)
    c. The dose does not exceed 8 mg/kg every 2 weeks
2. Gastric cancer
    a. Member's disease is advanced, recurrent, or metastatic OR use will be for palliative therapy for locoregional disease in members who are not surgical candidates
    b. Member has had an inadequate response to first-line therapy
    c. Ramucirumab will be used as monotherapy, in combination with paclitaxel, or in combination with irinotecan with or without fluorouracil
    d. The dose does not exceed 8 mg/kg every 2 weeks
3. Esophageal or Esophagogastric junction (EGJ) adenocarcinoma
    a. Member's disease is advanced, recurrent, or metastatic OR use will be for palliative therapy for locoregional disease in members who are not surgical candidates
    b. Member has had an inadequate response to first-line therapy
    c. Ramucirumab will be used as monotherapy, in combination with paclitaxel, or in combination with irinotecan with or without fluorouracil
    d. The dose does not exceed 8 mg/kg every 2 weeks
4. Hepatocellular Carcinoma
    a. Member has progressive disease
    b. **ONE** of the following:
        i. Member has unresectable disease and is not a transplant candidate

ii. Member has extrahepatic/metastatic disease and ineligible for resection, transplant, or locoregional therapy

c. Member has an alpha fetoprotein (AFP) of greater than or equal to 400 ng/mL

d. Ramucirumab will be used as monotherapy

e. The dose does not exceed 8 mg/kg every 2 weeks

5. Mesothelioma

a. Member has pleural mesothelioma, including pericardial mesothelioma or tunica vaginalis testis mesothelioma

b. Ramucirumab will be used as subsequent systemic therapy in combination with gemcitabine

c. The dose does not exceed 8 mg/kg every 2 weeks

6. Non-small cell lung cancer

a. Member's disease is recurrent, advanced, or metastatic

b. **ONE** of the following:

i. Ramucirumab will be used in combination with docetaxel following disease progression on a first-line cytotoxic regimen

ii. Ramucirumab will be used in combination with erlotinib for EGFR exon 19 deletion or exon 21 L858R disease as either first line therapy or continuation of therapy following disease progression on combination erlotininb and ramucirumab

c. The dose does not exceed 10 mg/kg every 3 weeks OR 10 mg/kg every 2 weeks if used in combination with erlotinib

7. Rectal cancer

a. Member's disease is advanced or metastatic

b. Use will be in combination with either of the following:

i. Irinotecan

ii. FOLFIRI (fluorouracil, leucovorin, and irinotecan)

c. The dose does not exceed 8 mg/kg every 2 weeks

8. Thymic Carcinoma

a. Member's disease is recurrent, advanced, or metastatic OR use will be for preoperative or postoperative treatment in resection of thymic carcinoma

b. Use will be as monotherapy or in combination with carboplatin and paclitaxel

c. The dose does not exceed 10 mg/kg every 3 weeks

9. Other FDA-approved or NCCN supported diagnosis (not previously listed above)

a. Member meets **ONE** of the following:

i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

b. The dose does not exceed 8 mg/kg every 2 weeks

Duration of approval: 6 months

Continuation of ramucirumab (Cyramza) meets the definition of **medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for treatment of colon cancer, gastric cancer, esophageal or esophagogastric junction (EGJ) adenocarcinoma, hepatocellular carcinoma, mesothelioma, NSCLC, rectal cancer, thymic carcinoma, or other FDA-approved or NCCN supported diagnosis, **OR** the member previously met all indication-specific initiation criteria
2. Member has a known sensitizing EGFR mutation (NSCLC) or member's disease has not progressed during treatment with ramucirumab
3. The dose does not exceed diagnosis specific limitation:
    a. Colon cancer: 8 mg/kg every 2 weeks
    b. Gastric cancer: 8 mg/kg every 2 weeks
    c. Gastro-esophageal junction adenocarcinoma: 8 mg/kg every 2 weeks
    d. Hepatocellular carcinoma: 8 mg/kg every 2 weeks
    e. Mesothelioma: 8 mg/kg every 2 weeks
    f. Non-small cell lung cancer: 10 mg/kg every 3 weeks **OR** 10 mg/kg every 2 weeks if used in combination with erlotinib
    g. Rectal cancer: 8 mg/kg every 2 weeks
    h. Hepatocellular carcinoma: 8 mg/kg every 2 weeks
    i. Thymic carcinoma: 10 mg/kg every 3 weeks

Duration of approval: 6 months

DOSAGE/ADMINISTRATION:

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FDA-approved

- Gastric cancer, Gastro-esophageal junction adenocarcinoma: 8 mg/kg IV every 2 weeks
- Non-small cell lung cancer: 10 mg/kg IV every 3 weeks
- Premedicate with IV histamine H1-antagonist (e.g., diphenhydramine) prior to each infusion

Dose Adjustments

Infusion Related Reactions (IRR)

- Reduce the infusion rate by 50% for Grade 1 or 2 IRRs
- Permanently discontinue for Grade 3 or 4 IRRs

Hypertension

- Interrupt for severe hypertension until controlled with medical management

- Permanently discontinue for severe hypertension that cannot be controlled with antihypertensive therapy

Proteinuria

- Interrupt or urine protein levels ≥2 g/24 hours. Reinitiate treatment at a reduced dose of 6 mg/kg (8 mg/kg if NSCLC) once the urine protein level returns to <2 g/24 hours. If the protein level ≥2 g/24 hours reoccurs, interrupt and reduce the dose to 5 mg/kg (6 mg/kg if NSCLC) once the urine protein level returns to <2 g/24 hours.
- Permanently discontinue for urine protein level >3 g/24 hours or in the setting of nephrotic syndrome

Wound Healing Complications

- Interrupt prior to scheduled surgery until the wound is fully healed

Arterial Thromboembolic Events, Gastrointestinal Perforation, or Grade 3 or 4 Bleeding

- Permanently discontinue

Drug Availability

100 mg/10 mL solution, single-dose vial; 500 mg/50 mL solution, single-dose vial

PRECAUTIONS:

Boxed Warning

- Hemorrhage: Increased the risk of hemorrhage, including severe and sometimes fatal hemorrhagic events

Contraindications

None

Precautions/Warnings

- Arterial Thromboembolic Events
- Hypertension
- Gastrointestinal perforation
- Impaired Wound Healing
- Clinical Deterioration in Patients with Cirrhosis
- Reversible Posterior Leukoencephalopathy Syndrome

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9308	Injection, ramucirumab, 5 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

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
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.8	Malignant neoplasm of other specified sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified site
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
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 colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of other sites of rectum, rectosigmoid junction, and anus
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 – C34.92	Malignant neoplasm of bronchus or lung
C37	Primary or metastatic malignant neoplasm involving the thymus
C45.0	Mesothelioma of pleura
C45.2	Mesothelioma of pericardium
C45.7	Mesothelioma of other sites
C45.9	Mesothelioma, unspecified
C78.00 – 78.02	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
D37.2	Neoplasm of uncertain behavior of small intestine
D37.4	Neoplasm of uncertain behavior of colon
D37.5	Neoplasm of uncertain behavior of rectum
D37.8	Neoplasm of uncertain behavior of other specified digestive organs
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled POSITION STATEMENT.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

Table 2: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Table 3: Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 09/09/26.

GUIDELINE UPDATE INFORMATION:

09/15/14	New Medical Coverage Guideline.
02/15/15	Revision to guideline; consisting of description, position statement, dosage, administration, coding.
08/15/15	Review and revision to guideline; consisting of position statement, coding, references.
11/01/15	Revision: ICD-9 Codes deleted.
01/01/16	Annual HCPCS coding update: added code J9308 and deleted codes C9025 and J9999.
07/15/16	Revision to guideline; consisting of updating position statement and ICD10 codes.
08/15/16	Review and revision to guideline; consisting of updating position statement and references.
08/15/17	Review and revision to guideline consisting of updating position statement and references.
10/15/18	Review and revision to guideline; consisting of updating position statement and references.
03/15/19	Revision to guideline; updated position statement.
10/15/19	Review and revision to guideline consisting of updating description, position statement, references.
02/15/20	Revision to guideline; updated position statement.
10/15/20	Review and revision to guideline, consisting of updating references.
04/15/21	Revision to guideline; updated position statement.
10/15/21	Review and revision to guideline, consisting of updating position statement and references.
10/15/23	Review and revision to guideline, consisting of updating position statement and references.
10/15/24	Review and revision to guideline, consisting of updating position statement and references.
10/15/25	Review and revision to guideline, consisting of updating position statement and references.
06/01/26	Revision: Added Drug Waste Reduction statement to the Position Statement.
10/15/26	Review and revision to guideline, consisting of updating position statement, coding, and references.