CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL ONCOLOGY

Ramucirumab (Cyramza®)

Version: 1.0

EFFECTIVE DATE: 1/1/2024

NantHealth® | Eviti®

Please note the following:

Ramucirumab (Cyramza®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Ramucirumab (Cyramza): Discussion

Ramucirumab is a recombinant human IgG1 monoclonal antibody that binds to VEGFR-2 and acts as an antagonist to VEGF-A, VEGF-C, and VEGF-D. Inhibition of receptor activation impedes VEGF-A–stimulated proliferation and migration of endothelial cells, which ultimately results in reduced tumor vascularity and growth.

Angiogenesis is an important process in cancer development and growth. Angiogenesis is primarily driven by the interactions between vascular endothelial growth factor (VEGF) ligands and VEGF receptors (VEGFRs). The VEGF ligands include VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PGF). [1]

Ramucirumab is approved by the Food and Drug Administration (FDA) for the following:

1. As a single agent or in combination with paclitaxel, for the treatment of advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy; OR
2. In combination with erlotinib, for first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations; OR
3. In combination with docetaxel, for treatment of metastatic non-small cell lung cancer 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 ramucirumab; OR
4. In combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and fluoropyrimidine; OR
5. As a single agent, for the treatment of hepatocellular carcinoma in patients who have an alpha-fetoprotein of > 400 ng/mL and have been treated with sorafenib. [2]

Note: The National Comprehensive Cancer Network (NCCN) endorses ramucirumab in the following cancer types: colon, esophageal/esophagogastric junction, gastric, hepatocellular, pleural mesothelioma, non-small cell lung, and rectal. [3,4,5,6,7,8,9]

Ramucirumab: Definitions

- **Child-Pugh Class A -** A scoring system for assessing the prognosis of chronic liver disease, mainly cirrhosis. It provides a forecast of the increasing severity of liver disease and the expected survival rate. Class A is the least severe liver disease.
- **Deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H)** - When the microsatellite DNA segments in cancer cells show changes (mutations), this indicates that the tumor cells are deficient in the repair of the mismatch errors. These cancers have microsatellite instability (also called MSI-High, MSI-H, or mismatch repair deficiency, dMMR).
- **Epidermal growth factor receptor (EGFR) exon 19 deletion mutation -** The most common activating mutation in advanced non-small cell lung cancer and is associated with sensitivity to treatment with EGFR tyrosine kinase inhibitors (TKIs).
- **Epidermal growth factor receptor (EGFR) exon 21 L858R point mutation -** Another frequently detected EGFR mutation in non-small cell lung cancer that is associated with sensitivity to treatment with EGFR tyrosine kinase inhibitors (TKIs).
- **Food and Drug Administration (FDA) -** The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **Karnofsky Score** - A 0-100 score on the Karnofsky Functional Scale, an assessment of a patient's status and ability to carry out activities of daily living. It is a measure that helps determine the ability of the patient to tolerate therapies such as chemotherapy. It can be used to assess treatments since scores decrease when diseases such as cancer progress.
- **National Comprehensive Cancer Network (NCCN) -** An alliance of 32 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.
- **Proficient mismatch repair/microsatellite-stable (pMMR/MMS) -** When microsatellite DNA segments are unchanged (not mutated), the tumor cells are considered microsatellite stable (MSS) or have proficient mismatch repair. MSS cancers have normal levels of mismatch repair gene and protein expression and are able to correct DNA mismatch repair errors proficiently.
- **T790M negative mutation -** Absence of most common resistance mutation after treatment with EGFR tyrosine kinase inhibitors (TKIs).
- **Vascular endothelial growth factor (VEGF) -** A signaling protein that promotes the growth of new blood vessels. VEGF forms part of the mechanism that restores the blood supply to cells and tissues when they are deprived of oxygenated blood due to compromised blood circulation.

Ramucirumab: Policy

Ramucirumab will be considered for coverage when the following criteria are met:

Colon Cancer (Adenocarcinoma)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Adjuvant treatment in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) or irinotecan for unresectable metachronous metastases for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) that converted to resectable disease after initial treatment; OR
4. Initial treatment for unresectable metachronous metastases in combination with irinotecan, or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, or deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) and the patient is not a candidate for immunotherapy and received previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; OR
5. Subsequent therapy for progression of advanced or metastatic disease for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen in patients not previously treated with irinotecan-based therapy.

Note: Biologic therapy is only appropriate for the continuation of a favorable response from conversion therapy.

Appendiceal Cancer (Adenocarcinoma)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Subsequent therapy for progression of advanced or metastatic disease for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen in patients not previously treated with irinotecan-based therapy. [3]

Esophageal and Esophagogastric Junction Cancers (Adenocarcinoma)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Palliative therapy for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease and Karnofsky performance score >60% or ECOG performance score < 2 as second-line or subsequent therapy in combination with paclitaxel, in combination with irinotecan with or without fluorouracil, or as a single agent [4]

Gastric Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Palliative therapy for locoregional disease in patients who are not surgical candidates OR have unresectable locally advanced, recurrent, or metastatic disease and Karnofsky performance score >60% or ECOG performance score <2 as second-line or subsequent therapy in combination with paclitaxel, in combination with irinotecan with or without fluorouracil, or as a single agent [5]

Hepatocellular Carcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Subsequent treatment as a single agent for progressive disease in those with alpha-fetoprotein (AFP) >400 ng/mL and Child-Pugh Class A only who have one of the following:
    a) Unresectable disease and are not a transplant candidate
    b) Liver-confined disease, inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic disease
    c) Metastatic disease or extensive liver tumor burden [6]

Mesothelioma: Pleural

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Subsequent systemic therapy in combination with gemcitabine

Note: May be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma. [7]

Non-Small Cell Lung Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Therapy in combination with erlotinib for EGFR exon 19 deletion or exon 21 L858R recurrent, advanced, or metastatic disease for one of the following:
    a) First-line therapy
    b) Continuation of therapy following disease progression on a combination of erlotinib and ramucirumab for asymptomatic disease, symptomatic brain lesions, or symptomatic systemic limited progression (if T790M negative); OR

4. Subsequent systemic therapy in combination with docetaxel (if not already given) for recurrent, advanced, or metastatic disease in those with performance status 0-2. [8]

Rectal Cancer (Adenocarcinoma)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Adjuvant treatment in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) or irinotecan for unresectable metachronous metastases for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only that converted to resectable disease after initial treatment; OR
4. Initial treatment for unresectable metachronous metastases in combination with irinotecan, or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, and previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; OR
5. Subsequent therapy for progression of advanced or metastatic disease for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for, or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen in patients not previously treated with irinotecan-based therapy [9]

Note:

1. Biologic therapy is only appropriate for a continuation of a favorable response from conversion therapy.
2. Coverage of ramucirumab will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation, or when all criteria are met.

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Ramucirumab: References

1. Ramucirumab: A New Therapy for Advanced Gastric Cancer. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4577036. Accessed May 18, 2023.
2. Cyramza® (Ramucirumab) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125477s042lbl.pdf. Accessed May 18, 2023.
3. National Comprehensive Cancer Network Guidelines. Colon Cancer (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed May 18, 2023.
4. National Comprehensive Cancer Network Guidelines. Esophageal and Esophagogastric Junction Cancers (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed May 5, 2023.
5. National Comprehensive Cancer Network Guidelines. Gastric Cancer (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed May 5, 2023.
6. National Comprehensive Cancer Network Guidelines. Hepatocellular Carcinoma (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf. Accessed May 5, 2023.
7. National Comprehensive Cancer Network Guidelines. Mesothelioma: Pleural (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/meso_pleural.pdf. Accessed May 5, 2023.
8. National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer (Version 3.2023). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed May 5, 2023.
9. National Comprehensive Cancer Network Guidelines. Rectal Cancer (Version 2.2023) https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed May 18, 2023.

Ramucirumab: Coding (CPT®, ICD 10 and HCPCS) *

* Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

CODE	DESCRIPTION
C15.3 – C15.9	Malignant neoplasm of the esophagus
C18.2 – C19	Malignant neoplasm of the colon
C20.0	Malignant neoplasm of the rectum

C22.0	Hepatocellular carcinoma
C45.0	Pleural mesothelioma
Z85.118	Non-small cell lung cancer
J9308	Ramucirumab (Cyramza)

Ramucirumab: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	5/31/2023
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	10/5/2023
6	Revision Changes:	