CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL ONCOLOGY

Ramucirumab (Cyramza®)

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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.

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Ramucirumab (Cyramza®)

Discussion

Ramucirumab is a recombinant human immunoglobulin IgG1 monoclonal antibody that binds to a vascular endothelial growth factor receptor (VEGFR2) and blocks the binding of VEGFR ligands, 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.

Common adverse reactions include hypertension, diarrhea, fatigue/asthenia, neutropenia, epistaxis, proteinuria, alopecia, increased alanine aminotransferase, increased aspartate aminotransferase, anemia, thrombocytopenia, stomatitis/mucosal inflammation, decreased appetite, peripheral edema, abdominal pain, nausea, ascites, hypoalbuminemia, and hyponatremia. Clinically significant adverse reactions include hemorrhage, gastrointestinal perforations, impaired wound healing, arterial thromboembolic events, hypertension, infusion-related reactions, worsening of pre-existing hepatic impairment, posterior reversible encephalopathy syndrome (PRES), proteinuria (including nephrotic syndrome), and thyroid dysfunction. Symptoms of PRES seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension.

Ramucirumab is approved by the Food and Drug Administration (FDA) for the following cancer types: gastric, non-small cell lung, colorectal, and hepatocellular.[1] The National Comprehensive Cancer Network (NCCN) endorses ramucirumab in the following cancer types: colon, esophageal and esophagogastric junction, gastric, hepatocellular, pleural mesothelioma, non-small cell lung, rectal, and thymomas and thymic.[2,3,4,5,6,7,8,9]

Definitions

- **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).[10]
- **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.[11]
- **Karnofsky Score** - A 0 to 100 score which is used as 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.[12]
- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than thirty leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN

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consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.[13]

- **Posterior Reversible Encephalopathy Syndrome (PRES)** - A rare condition marked by headaches, vision problems, mental changes, seizures, and swelling in the brain. Symptoms usually come on quickly and can be serious and life threatening. When treated, symptoms often go away within days or weeks. It may occur in patients with certain conditions, such as high blood pressure, eclampsia, severe infection, kidney disease, and certain autoimmune diseases. It may also occur in patients treated with certain anticancer drugs and immunosuppressive drugs. Also called reversible posterior leukoencephalopathy syndrome (RPLS).[14]
- **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.[10]
- **T790M Mutation** - A specific secondary point mutation in the EGFR (epidermal growth factor receptor) gene, where the amino acid threonine (T) at position 790 is replaced by methionine (M). This mutation is associated with acquired resistance to tyrosine kinase inhibitors.[15]
- **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.[16]

Policy

Coverage will be considered for FDA approved indications and for NCCN category 1, 2A, or 2B recommendations when all criteria are met:

Colon Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** Required criteria coverage:

3. In combination with FOLFIRI (irinotecan, folinic acid, and fluorouracil), for metastatic colorectal cancer with progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine;[1] OR

For **NCCN** required criteria coverage:

4. Second-line and subsequent therapy for progression of advanced or metastatic disease (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progressed on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb]) in combination with irinotecan or

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with FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen, if not previously given and not previously treated with irinotecan-based therapy; OR

5. Adjuvant treatment in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) or irinotecan for unresectable metachronous metastases (pMMR/MMS only or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb]) that converted to resectable disease after initial treatment. Biologic therapy is only appropriate for continuation of favorable response from conversion therapy; OR
6. Initial treatment for unresectable metachronous metastases (pMMR/MMS ordMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb) and not a candidate for immunotherapy) and previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPEOX (capecitabine and oxaliplatin) within the past 12 months in combination with one of the following:
   a) Irinotecan
   b) FOLFIRI (fluorouracil, leucovorin, and irinotecan); OR

Appendiceal Adenocarcinoma

For **NCCN** required criteria coverage:

7. Second-line and subsequent therapy for progression of advanced or metastatic disease (pMMR/MMS or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb) in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen if not previously treated with irinotecan-based therapy or not previously treated with oxaliplatin or irinotecan.[2]

Esophageal and Esophagogastric Junction Cancers

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** Required criteria coverage:

3. Single agent or in combination with paclitaxel, for advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine or platinum-containing chemotherapy;[1] OR

For **NCCN** required criteria coverage:

4. Palliative therapy if not surgical candidate or have unresectable locally advanced, recurrent, or metastatic disease and a 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.[3]

Gastric Cancer

1. At least 18 years of age; AND

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2. Prescribed by or in consultation with an oncologist; AND

For **FDA** Required criteria coverage:

3. Single agent or in combination with paclitaxel for advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine or platinum-containing chemotherapy;[1] OR

For **NCCN** required criteria coverage:

4. Palliative therapy for locoregional disease if not surgical candidate or have unresectable locally advanced, recurrent, or metastatic disease (including peritoneal only metastatic disease, including positive cytology) and a Karnofsky performance score ≥60% or ECOG performance score ≤2 as second-line or subsequent therapy in combination with irinotecan with or without fluorouracil, in combination with paclitaxel, or as a single agent.[4]

Hepatocellular Carcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** Required criteria coverage:

3. Single agent with an alpha fetoprotein (AFP) of ≥400 ng/mL and previous treatment with sorafenib;[1] OR

For **NCCN** required criteria coverage:

4. Subsequent-line systemic therapy as a single agent if progressive on or after systemic therapy and AFP ≥ 400 ng/mL.[5]

Pleural Mesothelioma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Subsequent systemic therapy in combination with gemcitabine

   Note: May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.[6]

Non-Small Cell Lung Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** Required criteria coverage:

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3. In combination with erlotinib as first-line for metastatic disease with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations; OR
4. In combination with docetaxel for metastatic disease with progression on or after platinum-based chemotherapy

   Note: 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 ramucirumab;[1] OR

For **NCCN** required criteria coverage:

5. Therapy in combination with erlotinib for EGFR exon 19 deletion or exon 21 L858R for recurrent, advanced, or metastatic disease for one of the following:
   a) First-line therapy (if EGFR mutation discovered prior to first-line systemic 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
6. Subsequent systemic therapy in combination with docetaxel (if not already given) for recurrent, advanced, or metastatic disease in those with performance status 0-2.[7]

Rectal Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** Required criteria coverage:

3. In combination with FOLFIRI (irinotecan, folinic acid, and fluorouracil), for metastatic colorectal cancer with progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine;[1] OR

For **NCCN** required criteria coverage:

4. Initial treatment for unresectable metachronous metastases (proficient mismatch repair/microsatellite-stable [pMMR/MMS] or deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb] and are not candidates for immunotherapy) and previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPEOX (capecitabine and oxaliplatin) within the past 12 months in combination with one of the following:
   a) Irinotecan
   b) FOLFIRI (fluorouracil, leucovorin, and irinotecan); OR
5. Adjuvant treatment in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) or irinotecan for unresectable metachronous metastases (pMMR/MMS or dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb] and are not candidates for immunotherapy) that converted to resectable disease after initial treatment. Biologic therapy is only appropriate for continuation of a favorable response from conversion therapy; OR

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6. Second-line and subsequent therapy for progression of advanced or metastatic disease in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen, if not previous given and not previously treated with irinotecan-based therapy (pMMR/MMS or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb]).[8]

Thymomas and Thymic Carcinomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required coverage criteria:

3. Preoperative systemic therapy for thymic carcinoma for surgically resectable disease if R0 resection is considered uncertain in combination with carboplatin and paclitaxel; OR
4. Postoperative systemic therapy for thymic carcinoma in combination with carboplatin and paclitaxel after R1 or R2 resection; OR
5. First-line systemic therapy for thymic carcinoma for recurrent, advanced, or metastatic disease in combination with carboplatin and paclitaxel for one of the following:
   a) Potentially resectable locally advanced disease
   b) Potentially resectable solitary metastasis or ipsilateral pleural metastasis
   c) Following surgery for solitary metastasis or ipsilateral pleural metastasis
   d) Medically inoperable/unresectable solitary metastasis or ipsilateral pleural metastasis
   e) Extrathoracic metastatic disease.[9]

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

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	Malignant neoplasm of the esophagus
C16	Malignant neoplasm of stomach

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C18.9	Malignant neoplasm of the colon, unspecified
C20	Malignant neoplasm of the rectum
C22.0	Liver cell carcinoma
C34	Malignant neoplasm of bronchus and lung
C37	Malignant neoplasm of thymus
C45.0	Mesothelioma of pleura
J9308	Injection, ramucirumab

Revision and Review History

No.	Description	Date
1	Original Effective Date:	1/1/2024
2	Policy Annual Review Dates:	5/31/2023, 10/15/2024, 10/2/2025
3	Department Owner:	Medical Affairs
4	NH Advisory Committee Approval Dates:	10/5/2023, 10/29/2024, 10/28/2025
5	Revision Changes	10/15/2024 - Added adverse reactions and one indication for NSCLC; v.1.0 10/2/2025 Added adverse reactions, 2 NCCN indications for colon, 3 NCCN for thymic, 1 FDA indication for NSCLC; modified 3 NCCN indications for rectal, 1 NCCN indication for gastric; v.2.0

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