Medical Drug Clinical Criteria

Subject:	Cyramza (ramucirumab)		
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Overview

This document addresses the use of Cyramza (ramucirumab). Cyramza is a monoclonal antibody that blocks the activation of vascular endothelial growth factor (VEGF) receptor-2 that is used to treat various types of cancer including gastric, lung, and colorectal cancer.

Cyramza is FDA approved, as a single agent or in combination with paclitaxel, to treat gastric or gastro-esophageal junction adenocarcinoma which has progressed on or after prior fluoropyrimidine- or platinum- containing chemotherapy. The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Cyramza in esophageal adenocarcinoma similar to the FDA approved use in gastric cancer.

Cyramza is also FDA approved to treat non-small cell lung cancer (NSCLC) in combination with docetaxel for those with disease progression on or after platinum-based chemotherapy. The labeled indication also notes that those with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA approved therapies for these aberrations prior to receiving Cyramza. Since approval for this indication, numerous other actionable mutations with FDA approved therapies have emerged. As a result, NCCN algorithm for NSCLC recommends patients with actionable mutations should receive targeted therapy for these mutations first, then (if needed) proceed to general systemic therapy including platinum-based therapy, then (if needed) proceed to Cyramza plus docetaxel. Cyramza also recently received FDA approval in combination with erlotinib as first line therapy for EGFR mutated NSCLC based on results of the RELAY trial (Nakagawa 2019).

Cyramza is FDA approved to treat metastatic colorectal cancer (mCRC) in combination with FOLFIRI regimen in those who progress after bevacizumab-, oxaliplatin-, and fluoropyrimidine-containing chemotherapy (i.e. FOLFOX/CAPEOX + bevacizumab). NCCN recommends Cyramza as an option after any oxaliplatin-based therapy, as well as after fluoropyrimidine regimens without oxaliplatin, regardless of previous bevacizumab use. However, NCCN notes that bevacizumab is the preferred anti-antiangiogenic agent and recognizes that Cyramza was studied after first-line therapy with fluoropyrimidine/oxaliplatin/bevacizumab (Tabernero 2015). NCCN notes that no data exists that suggest activity of FOLFIRI plus Cyramza in individuals who have progressed on FOLFIRI plus bevacizumab.

Cyramza recently received FDA approval for the treatment of advanced or unresectable hepatocellular carcinoma as subsequent treatment for progressive disease after sorafenib treatment, in patients with serum α–fetoprotein (AFP) concentrations of ≥ 400 ng/mL. The approval is based on the REACH (Zhu 2015) and REACH 2 (Zhu 2019) studies. The REACH study, which did not result in improved overall survival (OS) compared to placebo, included patients with any AFP level. However, subgroup analysis around baseline AFP level prompted the REACH 2 study which included only patients with baseline AFP of ≥ 400 ng/mL. In this study, the primary endpoint of improved median overall survival was statistically significant.

Cyramza has also shown benefit in urothelial carcinoma. While neither the FDA nor NCCN have endorsed Cyramza for this indication, the RANGE study (Petrylak 2017) indicated that participants treated with ramucirumab plus docetaxel experienced longer PFS compared with placebo plus docetaxel in select individuals with platinum-refractory advanced or metastatic urothelial carcinoma. Individuals in this study had received no more than one immune checkpoint inhibitor or prior systemic chemotherapy regimen and no prior systemic taxane therapy.

Other Uses

NCCN and other compendia do not support the use of Cyramza in breast cancer, metastatic melanoma, ovarian, fallopian tube or primary peritoneal cancer, pleural mesothelioma, or renal cell cancer.

Definitions and Measures

Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).

Disease Progression/ Progressive Disease (PD): Cancer that is growing, spreading, or getting worse

ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- 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, for example, 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

Fluoropyrimidine: A type of antimetabolite used to treat cancer. Examples include capecitabine, floxuridine, and fluorouracil (5-FU).

Non-small cell lung cancer: A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.

Refractory Disease: Illness or disease that does not respond to treatment.

Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Taxane: A type of mitotic inhibitor and antimicrotubule drug used to treat cancer that blocks cell growth by stopping mitosis (cell division).

Unresectable: Unable to be removed with surgery.

Urothelial carcinoma: A type of bladder cancer which occurs in the urinary tract system.

Vascular endothelial growth factor (VEGF): A substance made by cells that stimulates new blood vessel formation.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Cyramza (ramucirumab)

Requests for Cyramza (ramucirumab) may be approved if the following criteria are met:

I. Individual has a diagnosis of Hepatocellular Carcinoma and the following are met:
   A. Individual has inoperable or metastatic disease (NCCN 1); **AND**
   B. Individual has had disease progression on or after prior treatment with Sorafenib; **AND**
   C. Ramucirumab is used as a single agent; **AND**
   D. Individual has a baseline serum α–fetoprotein (AFP) concentrations of ≥ 400 ng/mL at initiation of therapy;

OR

II. Individual has a diagnosis of Esophageal, Gastric, or Gastroesophageal Junction Adenocarcinoma and the following are met:
   A. Individual has advanced (non-resectable) or metastatic disease; **AND**
   B. Ramucirumab is used as a single agent or in combination with paclitaxel, or in combination with irinotecan; **AND**
   C. Individual has had disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy;

OR

III. Individual has a diagnosis of metastatic Non-small Cell Lung Cancer (NSCLC) and the following are met (Label, NCCN 2A):
   A. Ramucirumab is used in combination with docetaxel; **AND**
   B. Individual meets either of the following:

1. Individual does not have presence of actionable molecular markers*, *and* the disease has progressed on or after platinum-containing chemotherapy; **OR**
2. Individual has presence of actionable molecular markers* and *both* of the following criteria are met:
    a. Disease has progressed on a U.S. Food & Drug Administration (FDA)-approved therapy for these mutations prior to receiving ramucirumab; **AND**
    b. Disease has progressed on or after platinum-containing chemotherapy;

OR

IV. Individual has a diagnosis of metastatic Non-small Cell Lung Cancer (NSCLC) and the following are met:
    A. Individual has an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation with test results confirmed; **AND**
    B. Ramucirumab is used as first line therapy in combination with erlotinib;

OR

V. Individual has a diagnosis of metastatic Colorectal Cancer and the following are met:
    A. Individual has had disease progression on or after prior bevacizumab- (or bevacizumab biosimilar-), oxaliplatin-, and fluoropyrimidine- containing chemotherapy; **AND**
    B. Ramucirumab is used in combination with irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI);

OR

VI. Individual has a diagnosis of Urothelial Cancer originating from the bladder, urethra, ureter, or renal pelvis and the following are met (Petrylak 2017):
    A. Individual is 18 years of age or older; **AND**
    B. Ramucirumab is used in combination with docetaxel; **AND**
    C. Individual has a current Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; **AND**
    D. Individual has locally advanced, unresectable, or metastatic disease that has progressed after platinum-containing chemotherapy (cisplatin or carboplatin); **AND**
    E. Individual has received treatment with no more than one immune checkpoint inhibitor (such as, atezolizumab, avelumab, durvalumab, nivolumab or pembrolizumab); **AND**
    F. Individual has received treatment with no more than one prior systemic chemotherapy regimen in the relapsed or metastatic setting; **AND**
    G. Individual has received no prior systemic taxane therapy in any setting (that is, neoadjuvant, adjuvant, or metastatic).

***Note:** Actionable molecular markers include EGFR, ALK, ROS1, BRAF, NTRK, MET and RET mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NCCN 1, 2A).

Requests for Cyramza (ramucirumab) may not be approved for the following:

I. Ramucirumab is used for colorectal cancer in combination with the same irinotecan-based regimen that was previously used in combination with bevacizumab (or bevacizumab biosimilar); **OR**
II. The following diagnoses:
    A. Breast cancer; **OR**
    B. Metastatic melanoma; **OR**
    C. Ovarian, fallopian tube or primary peritoneal cancer; **OR**
    D. Renal cell cancer; **OR**
III. May not be approved if all the above criteria have not been met or for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9308	Injection, ramucirumab, 5 mg [Cyramza]

ICD-10 Diagnosis

C15.3-C15.9	Malignant neoplasm of esophagus
C16.0-C16.9	Malignant neoplasm of stomach
C18.0-C20	Malignant neoplasm of colon, rectosigmoid junction, rectum

C22.0	Hepatocellular carcinoma
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C65.1-C65.9	Malignant neoplasm of renal pelvis
C66.1-C66.9	Malignant neoplasm of ureter
C67.0-C67.9	Malignant neoplasm of bladder
C68.0	Malignant neoplasm of urethra
C78.00-C78.02	Secondary malignant neoplasm of lung
C78.5	Secondary malignant neoplasm of large intestine and rectum
C78.89	Secondary malignant neoplasm of other digestive organs
Z85.01	Personal history of malignant neoplasm of esophagus
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.51	Personal history of malignant neoplasm of bladder
Z85.53-Z85.59	Personal history of malignant neoplasm of renal pelvis, ureter, other urinary tract organ

Document History

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Document History:

- 02/24/2023 – Annual Review: add combination therapy with irinotecan, wording and formatting. Coding Reviewed: No changes.
- 02/25/2022– Annual Review: wording and formatting changes. Coding Reviewed: No changes.
- 02/19/2021– Annual Review: Update criteria for subsequent therapy in lung cancer to include any actionable molecular marker; update references. Coding Reviewed: No changes.
- 02/21/2020– Annual Review: Add new NCCN recommendation for first line treatment of NSCLC in combination with erlotinib; specify use as a single agent for hepatocellular cancer; add may not be approved language regarding previous irinotecan+bevacizumab regimens for consistency; add biosimilar reference. Coding reviewed: No changes.
- 05/17/2019– Annual Review: First review of Cyramza clinical criteria. Add treatment of hepatocellular carcinoma to clinical criteria. Minor wording and formatting updates. Add references for off label criteria. Coding Reviewed: Add ICD-10 for Hepatocellular carcinoma C22.0, and C22.9 Malignant neoplasm of liver, not specified as primary or secondary.

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    c. Non-Small Cell Lung Cancer. V1.2023. Revised December 22, 2022.
    d. Colon Cancer. V2.2022. Revised October 27, 2022.
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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.