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Ascension

Ramucirumab

(Cyramza®) J9308 (5 mg)

Covered with prior authorization

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

- Individual has a diagnosis of Hepatocellular Carcinoma and the following are met:
  - Individual has inoperable or metastatic disease (NCCN 2A); **AND**
  - Individual has had disease progression on or after prior treatment with Sorafenib; **AND**
  - Ramucirumab is used as a single agent; **AND**
  - Individual has a baseline serum α–fetoprotein (AFP) concentration of ≥ 400 ng/mL at initiation of therapy;

OR

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

OR

- Individual has a diagnosis of metastatic Non-small Cell Lung Cancer (NSCLC) and the following are met (Label, NCCN 2A):
  - Ramucirumab is used in combination with docetaxel; **AND**
  - Individual meets either of the following:
    - Individual does not have presence of actionable molecular markers*, and the disease has progressed on or after platinum-containing chemotherapy; **OR**
    - Individual has presence of actionable molecular markers* and both of the following criteria are met:
      - Disease has progressed on a U.S. Food & Drug Administration (FDA)-approved therapy for these mutations prior to receiving ramucirumab; **AND**
      - Disease has progressed on or after platinum-containing chemotherapy;

OR

- Individual has a diagnosis of metastatic Non-small Cell Lung Cancer (NSCLC) and the following are met:
  - Individual has an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation with test results confirmed; **AND**

- Ramucirumab is used as first line therapy in combination with erlotinib;

OR

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

OR

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

OR

- Individual has diagnosis of Hepatocellular Carcinoma
  - Individual is 18 years of age or older; **AND**
  - Have an alpha-fetoprotein (AFP) of ≥ 400 ng/mL; **AND**
  - Treated with sorafenib

***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 if the above criteria are not met and for all other indications not included above.

Initial and renewal authorizations are for up to 12 months.

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Annual reauthorizations will require medical chart documentation that the patient has been seen within the past 12 months and that markers of disease are improved by therapy.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Exclusion criteria:

- Cyramza® (ramucirumab) may not be approved when the above criteria are not met and for all other indications.
- Doses, durations, or dosing intervals that exceed FDA maximum limits for any FDA-approved indication or are not supported by industry-accepted practice guidelines or peer-reviewed literature for the relevant off-label use.
- Individuals with significant known risk factors unless the record provides an assessment of clinical benefit that outweighs the risk.
- 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).
- The following diagnoses:
    - Breast cancer; **OR**
    - Metastatic melanoma; **OR**
    - Ovarian, fallopian tube or primary peritoneal cancer; **OR**
    - Renal cell cancer.

U.S. Food and Drug Administration:
This section is to be used for informational purposes. FDA approval alone is not a basis for coverage. 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, the 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.

Key References Accessed 8/2022:

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm.
2. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
3. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small cell lung cancer (RELAY): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019; 20:1655-1669.
4. NCCN Clinical Practice Guidelines in Oncology™. For additional information visit the NCCN website: http://www.nccn.org/index.asp.
    a. Esophageal and Esophagogastric Junction Cancers. V1.2022. Revised December 21, 2021.
    b. Gastric Cancer V1.2022. Revised December 20, 2021.
    c. Non-Small Cell Lung Cancer. V1.2022. Revised December 7, 2021.

d. Colon Cancer. V3.2021. Revised September 10, 2021.
e. Rectal Cancer V2.2021. Revised September 10, 2021.
f. Hepatobiliary Cancers. V5.2021. Revised September 21, 2021.

5. Petrylak DP, de Wit R, Chi KN, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial. Lancet. 2017; 390(10109):2266-2277.
6. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol. 2015; 16(5):499-508. Correction: 2015; 16(6):e262.
7. Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomized, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015; 16(7):859-870.
8. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019; 20(2):282-296.

Date	**Summary of Changes**
August 2022	Criteria for use summary developed by the Ascension Medical Specialty Prior Authorization Team.
September 2022	Criteria for use summary approved by the Ascension Ambulatory Care Expert Review Panel.
October 2022	Criteria for use summary approved by the Ascension Therapeutic Affinity Group.

If you have questions, call 833-980-2352 to speak to a member of the Ascension Rx prior authorization team, or email your questions to smarthealthspecialty@ascension.org.