I. PURPOSE

To define and describe the accepted indications for Cyramza (ramucirumab) usage in the treatment of cancer

II. DEFINITIONS

Cyramza (ramucirumab): is a vascular endothelial growth factor (VEGF) receptor 2 antagonist that inhibits ligand-stimulated activation of the VEGF receptor 2, ligand-induced proliferation, and migration of human endothelial cells. When activation of VEGFR2 by its ligands is inhibited, cell proliferation and migration of human endothelial cells is inhibited. Ramucirumab works differently than bevacizumab, another VEGF inhibitor, in that bevacizumab binds to the ligand, VEGF, preventing it from binding to VEGFR2/KDR. Ramucirumab binds to VEGF2, preventing the VEGF ligands from binding, and does not affect initial levels of VEGF. The mechanism of binding to VEGFR2 rather than VEGF may also induce less resistance, since endothelial cells are genetically stable.

Cyramza (ramucirumab) is FDA approved for the following: (1) As a single-agent or in combination with paclitaxel for the treatment of patients with advanced or metastatic, gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy, (2) In combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy, and (3) In combination with FOLFIRI, for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

Cyramza (ramucirumab) is available in 100 mg and 500 mg single dose vials.

III. POLICY

New Century is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century may be deemed as not approvable and therefore not reimbursable.

Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must follow CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.

Inclusion Criteria: Cyramza (ramucirumab) may be considered medically necessary when any of the following selection criteria is met:

1. Gastric and Gastroesophageal Junction Cancers
a. The member has locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma AND
b. Cyramza (ramucirumab) is being used with ALL of the following conditions:
   i. As a single agent or in combination with paclitaxel
   ii. For member with ECOG performance score 2 or less
   iii. For disease progression, contraindications, or intolerance to prior fluoropyrimidine-
        or platinum-containing chemotherapy (i.e. common regimens include
        5FU/capecitabine and platinum with or without epirubicin or docetaxel).

2. **Non-Small Cell Lung Cancer (NSCLC)**
   a. The member has metastatic NSCLC and Cyramza (ramucirumab) is being used with ALL
      of the following conditions:
      i. As subsequent therapy in combination with docetaxel (if naïve) following
         progression on a cytotoxic regimen AND
      ii. Has an ECOG performance status 0-2.

3. **Colorectal Cancer**
   a. Cyramza (ramucirumab) is being used with ONE of the following conditions:
      i. In combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and
         irinotecan) regimen for members with unresectable metachronous metastases and
         previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX
         (capecitabine and oxaliplatin) within the past 12 months OR
      ii. As subsequent therapy for unresectable advanced or metastatic disease in
         combination with irinotecan or with FOLFIRI (fluorouracil, leucovorin, and
         irinotecan) regimen for disease not previously treated with irinotecan-based
         regimens.

**Exclusion Criteria:** Cyramza (ramucirumab) is not considered medically necessary when any of the following
selection criteria is met:

1. Cyramza (ramucirumab) is being used in members with a history of severe bleeding, blood clots,
   symptomatic heart disease, uncontrolled high blood pressure, stroke, active infection, kidney disease, or
   recent surgery.
2. Disease progression while taking Cyramza (ramucirumab).
3. Dosing exceeds single dose limit of Cyramza (ramucirumab) 10 mg/kg.
4. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be
   deemed as not approvable and therefore not reimbursable.

**IV. PROCEDURE**

Requests for Cyramza (ramucirumab) shall be reviewed for appropriateness per FDA approved product labeling,
the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical
guidelines, or CMS approved compendia.
1. **Dosage and Administration:**
   a. **Gastric and Gastroesophageal Junction Cancers:** 8 mg/kg IV over 60 minutes every 2 weeks as a single agent or in combination with paclitaxel 80 mg/m² intravenously once a week for 3 weeks of every 28-day cycle, repeat until disease progression or unacceptable toxicity. Prior to each ramucirumab infusion, premedicate all patients with an intravenous histamine H1 antagonist (i.e. diphenhydramine hydrochloride). For patients who have experienced a Grade 1 or 2 infusion reaction, also premedicate with dexamethasone (or equivalent) and acetaminophen prior to each ramucirumab infusion.
   b. **NSCLC:** 10 mg/kg administered by intravenous infusion over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion. Continue until disease progression or unacceptable toxicity.
   c. **Colorectal Cancer:** 8 mg/kg every 2 weeks administered by intravenous infusion over 60 minutes prior to FOLFIRI administration. Continue until disease progression or unacceptable toxicity.

2. **Dosage Adjustments**
   a. **Hepatic impairment, mild (total bilirubin within ULN and AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN and any AST):** No adjustment recommended.
   b. **Hepatic impairment, moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST):** No adjustment recommended.
   c. **Hepatic impairment, Child-Pugh class B or C cirrhosis:** Clinical deterioration has been reported.
   d. **Hypertension, severe:** interrupt therapy until controlled; permanently discontinue if not controlled with antihypertensive treatment.
   e. **Infusion-related reactions:** grade 1 or 2, reduce the rate of infusion by 50%; grade 3 or 4, permanently discontinue therapy.
   f. **Urine protein level 2 g/24 hours or greater:** interrupt therapy; once level returns to less than 2 g/24 hours, resume at a reduced dose of 6 mg/kg every 2 weeks; if level 2 g/24 hours or greater reoccurs, interrupt therapy again and once level returns to less than 2 g/24 hours, resume at a reduced dose of 5 mg/kg every 2 weeks.
   g. **Urine protein level greater than 3 g/24 hours or if nephrotic syndrome occurs:** permanently discontinue therapy.
   h. **Wound healing complications:** prior to scheduled surgery, interrupt ramucirumab until the wound is fully healed.

3. **Monitoring**
   a. **Improvement in signs or symptoms of advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma is indicative of efficacy.**
   b. **Proteinuria by dipstick urine analysis and serial urinalyses, if indicated, during therapy.**
   c. **Patients with a 2+ or greater urine dipstick reading should have a 24-hour urine collection performed.**
   d. **Blood pressure; at least every 2 weeks (more often if indicated).**
   e. **Infusion related reactions.**
V. APPROVAL AUTHORITY

1. Review – UM Department
2. Final Approval – UM Committee

VI. ATTACHMENTS

VII. REFERENCES