Effective for dates of service on and after February 26, 2018
Policy Replaced by Article A53426

BlueCross BlueShield of Alabama

"Unless otherwise noted, coverage for specific indications is effective the date of the FDA approval of that indication."
"Please check Approved by Governing Bodies for FDA approval date."

Name of Blue Advantage Policy:
Cyramza® (ramucirumab)

Policy #:	655	Effective Date:	December 13, 2016
Category:	Pharmacology	Latest Review Date:	October 2017

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Cyramza® (ramucirumab) is a fully human monoclonal antibody that targets and inactivates vascular endothelial growth factor receptor-2 (VEGFR-2). VEGFR-2 is an angiogenic receptor involved in the development of blood vessels in both normal cells and malignant tumors. Upon binding VEGFR, angiogenic ligands including VEGF-A, VEGF-B, and VEGF-C promote tumor growth and development of metastatic disease. Ramucirumab inhibits the activity of these ligands thereby impeding sufficient blood flow necessary for tumor growth and survival.

Ramucirumab carries a **black box warning** for increased risk of hemorrhage, gastrointestinal perforation, and impaired wound healing. Therapy with ramucirumab should be discontinued permanently in patients who experience severe bleeding and/or gastrointestinal perforation. It is recommended to withhold ramucirumab prior to surgery and discontinue therapy if a patient develops wound healing complications.

******"Unless otherwise noted, coverage for specific indications is effective the date of the FDA approval of that indication."***

Policy:

Effective for dates of service on or after November 1, 2018 refer to Palmetto Article A56141

Effective for dates of service on or after February 26, 2018 and prior to November 1, 2018 refer to Article A53426

Effective for dates of service on or after December 13, 2016 and prior to February 26, 2018:
Blue Advantage will treat **Cyramza® (ramucirumab)** as a **covered benefit** as **a single agent or in combination with paclitaxel** for the treatment of **advanced or metastatic gastric, esophageal, or gastro-esophageal junction adenocarcinoma** with disease progression that occurs on or after fluoropyrimidine- or platinum containing chemotherapy.

Blue Advantage will treat **Cyramza® (ramucirumab)** as a **covered benefit** when used **in combination with docetaxel** for the treatment of **metastatic or recurrent non-small cell lung cancer** with **ONE** of the following indications:

- The individual does not have EGFR or ALK positive NSCLC **AND** has had disease progression following treatment with platinum based chemotherapy.
  OR
- The individual has EGFR or ALK positive disease AND has had disease progression following treatment with an FDA approved regimen for treatment of those aberrations **AND** disease has progressed on or after platinum-containing chemotherapy.

Blue Advantage will treat **Cyramza® (ramucirumab)** as a **covered benefit** when used **in combination with irinotecan or with FOLFIRI** for treatment of **metastatic or recurrent colorectal cancer** that has progressed on or after prior therapy with bevacizumab, oxaliplatin, AND a fluoropyrimidine-containing chemotherapy.

Effective for dates of service May 1, 2016 through December 12, 2016
Blue Advantage will treat **Cyramza® (ramucirumab)** as a **covered benefit** as **a single agent or in combination with paclitaxel** for the treatment of **advanced gastric cancer, esophageal adenocarcinoma, or gastro-esophageal junction** with disease progression that occurs on or after prior fluoropyrimidine, platinum containing or taxane containing chemotherapy.

Blue Advantage will treat **Cyramza® (ramucirumab)** as a **covered benefit** when used **in combination with docetaxel** for the treatment of **metastatic or recurrent non-small cell lung cancer** with disease progression on or after platinum- based chemotherapy with **ONE** of the following indications:

- The individual has EGFR or ALK positive disease AND has had disease progression following treatment with:
    - An FDA approved regimen for treatment of EGFR positive NSCLC (e.g. Gilotrif or Tarceva), **OR**
    - An FDA approved regimen for treatment of ALK positive NSCLC (e.g. Xalkori or Zykadia)

  OR
- The individual does not have EGFR or ALK positive NSCLC **AND** has had disease progression following treatment with platinum based chemotherapy.

Blue Advantage will treat **Cyramza® (ramucirumab)** as a **covered benefit** when used **in combination with FOLFIRI or irinotecan** for treatment of **metastatic or recurrent colorectal cancer** that has progressed on or after prior therapy with bevacizumab, oxaliplatin, AND a fluoropyrimidine-containing chemotherapy.

Blue Advantage will treat **Cyramza® (ramucirumab)** as a **covered benefit** for **another FDA labeled indication** or **an NCCN 1 or 2A recommended indication** and the requested dose and duration is within the FDA labeling or NCCN 1 or 2A compendia supported dosing.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Gastric and Gastroesophageal Junction Adenocarcinoma
Ramucirumab is FDA indicated for use as a single agent for individuals with unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression during or after treatment with fluoropyrimidine- or platinum-containing chemotherapy. In addition,

ramucirumab is FDA indicated for use in combination with paclitaxel for the treatment of individuals with unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression during or after treatment with fluoropyrimidine- or platinum-containing chemotherapy.

The efficacy and safety of ramucirumab was evaluated in a multicenter, double-blind, randomized clinical study with 355 subjects (REGARD). The subjects had locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma and were previously treated with fluoropyrimidine- or platinum-containing chemotherapy. All subjects were randomized (2:1) to receive either single agent ramucirumab dosed at 8 mg/kg over a 60-minute infusion every 2 weeks or placebo administered every 2 weeks. The primary outcome measure was overall survival (OS). The median OS for the ramucirumab group was 5.2 months compared to 3.8 months for the placebo group (hazard ratio [HR]=0.78; 95% confidence interval [CI], 0.60-0.998; p=0.047). The study concluded these results indicate that the risk of death was significantly reduced (22% lower) in the treatment group compared with placebo. In addition, the study authors concluded ramucirumab had significant and positive treatment effects in individuals previously treated with fluoropyrimidine- or platinum-containing chemotherapy.

The second pivotal trial of ramucirumab was a multicenter, double-blind, randomized clinical study (phase III, RAINBOW trial) in which 656 subjects were randomized to receive either ramucirumab (8 mg/kg) plus paclitaxel (80 mg/m^2) (n=330) or placebo plus paclitaxel (80 mg/m^2) (n=335). Subjects were adults with advanced gastric or gastroesophageal junction adenocarcinoma and had had disease progression on or within 4 months after first-line chemotherapy. The primary outcome measure was overall survival (OS); secondary outcomes included progression-free survival (PFS) and the objective response rate. The median OS for the treatment group was 9.6 months (95% CI, 8.5-10.8) compared with 7.4 months for the placebo group (95% CI, 6.3-8.4) (HR=0.81; 95% CI, 0.68-0.96; p=0.017). The median PFS for the treatment group was 4.4 months (95% CI, 4.2-5.3) compared with 2.9 months for the placebo group (95% CI, 2.8-3.0) (HR=0.64; 95% CI, 0.54-0.75; p<0.001). The objective response rate for the treatment group was 28% (95% CI, 23-33) compared with 16% for the placebo group (95% CI, 13-22).

The most commonly observed adverse events (Grade 3 or higher) for those treated with ramucirumab combined with paclitaxel were fatigue, neutropenia, diarrhea, and epistaxis. Based on the OS data, the study authors concluded that ramucirumab combined with paclitaxel had significant and positive treatment effects in individuals previously treated with fluoropyrimidine- or platinum-containing chemotherapy.-

Al-Batran and colleagues (2016) subsequently reported an analysis of quality of life (QoL) and performance status outcomes for participants in the phase III RAINBOW trial. Participant-reported outcomes were assessed using the European Organization for Research and Treatment of Cancer QoL questionnaire (EORTC QLQ-C30) and the EuroQoL 5 dimensions health status questionnaire (EQ-5D-3L) at baseline and 6-week intervals. Performance status was assessed at baseline and day 1 of every cycle. The time to deterioration (TtD) in each QLQ-C30 scale was defined as randomization to first worsening of ≥ 10 points (on a 100-point scale) and TtD in performance status was defined as first worsening to ≥ 2. A total of 650 of 665 (98%)

randomized participants provided baseline QLQ-C30 and EQ-5D data, and 560 (84%) provided data from ≥ 1 post-baseline time point. Baseline scores were similar in both treatment arms for the 15 QLQ-C30 scales and the EQ-5D instrument. The participants treated with ramucirumab plus paclitaxel demonstrated a similar or longer TtD in the functioning and worsening of symptoms compared with participants treated with placebo plus paclitaxel. Ramucirumab plus paclitaxel was associated with improved outcomes in 14 of the 15 symptom scales compared with placebo plus paclitaxel, although statistical significance was only reached in 2 of the symptoms scales (that is, emotional function and nausea and vomiting). Diarrhea was the only QoL symptom with a non-favorable HR in the ramucirumab plus paclitaxel group. The analysis of QLC-C30 TtD data demonstrated that treatment with ramucirumab and paclitaxel was associated with a delay in TtD in performance status to ≥ 2 (HR=0.798; p=0.0941). EQ-5D scores were comparable between treatment arms, stable during treatment, and worsened at discontinuation. Based on these results, the authors suggest that second-line treatment with ramucirumab and paclitaxel prolongs survival and maintains QoL, lengthens the TtD of symptoms and functions, and slows performance status deterioration in individuals with metastatic gastric or gastroesophageal junction adenocarcinoma.

Esophageal Adenocarcinoma
Esophageal cancer is the sixth most common cause of cancer deaths worldwide with adenocarcinoma more common in North America and Western European countries. Esophageal adenocarcinoma originates most often in the lower third of the esophagus, and may involve the esophagogastric junction (EGJ). The National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines (CPGs) for esophageal and EGJ cancers includes a category 2A recommendation for use of ramucirumab as a single agent or in combination with paclitaxel as preferred second-line therapy for metastatic or locally advanced esophageal adenocarcinoma. The NCCN based this category 2A recommendation on uniform consensus and consideration of the recent FDA approvals of ramucirumab for EGJ and gastric adenocarcinoma. The peer-reviewed published literature for EGJ and gastric adenocarcinoma consists of the two pivotal clinical trials that included participants with EGJ adenocarcinoma, randomized to receive ramucirumab (n=60) or ramucirumab plus paclitaxel. To date, there are no randomized controlled trials published that evaluate the use of ramucirumab specifically for esophageal adenocarcinoma.

Non-Small Cell Lung Cancer (NSCLC)
Ramucirumab is FDA indicated, in combination with docetaxel, for the treatment of individuals with metastatic NSCLC who experienced disease progression on or after platinum-based chemotherapy. The FDA has also approved ramucirumab for the treatment of individuals with EGFR or ALK genomic tumor aberrations, who experienced disease progression on FDA approved therapy specific for these aberrations, before they receive treatment with ramucirumab.

Efficacy and safety of ramucirumab for this indication was evaluated in a randomized, double-blind study (REVEL) with 1253 subjects. All subjects had advanced or metastatic, squamous or non-squamous NSCLC, and had had disease progression during or after first-line platinum-based therapy for locally advanced or metastatic disease. Individuals were randomized to either ramucirumab (10 mg/kg) plus docetaxel (75 mg/m2) every 21 days, or placebo plus docetaxel (75 mg/m2) every 21 days. The subjects received a median of 4.5 doses of ramucirumab with a

median duration of 3.5 months. A total of 195 of 627 individuals (31%) received ramucirumab for at least 6 months. The primary outcome was overall survival (OS) and the secondary outcomes included progression free survival (PFS) and the objective response rate. The study results indicated OS was significantly improved in the ramucirumab treatment group compared with placebo. The median OS was 10.5 months for the treatment group compared with 9.1 months for the placebo group (HR=0.86; 95% CI, 0.75-0.98; p=0.024). Similarly, PFS was significantly improved in the treatment group compared with placebo. The median PFS was 4.5 months for the treatment group compared with 3.0 months for placebo (HR=0.76; 95% CI, 0.68-0.86; p<0.001).

The most commonly observed serious adverse events observed with ramucirumab plus docetaxel were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). In individuals older than 65 years, there were 18 (8%) deaths during treatment or within 30 days of ending treatment compared with 9 (4%) deaths for placebo plus docetaxel. In individuals younger than age 65, there were 13 (3%) deaths during treatment or within 30 days of ending treatment with ramucirumab plus docetaxel compared with 26 (6%) deaths for placebo plus docetaxel. Treatment with ramucirumab resulted in significantly greater number of participants who discontinued treatment (9%) compared with the placebo group (5%).

Colorectal Cancer
Ramucirumab is FDA indicated for use in combination with irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) for the treatment of metastatic colorectal cancer following progression after treatment with bevacizumab-, oxaliplatin-, and fluoropyrimidine-containing chemotherapy. Efficacy and safety ramucirumab for the treatment of this diagnosis was evaluated in a single clinical trial (RAISE). The RAISE trial was a phase III, randomized, double-blind, trial of subjects with metastatic colorectal cancer that progressed during treatment with, or within 6 months of discontinuation, of bevacizumab-, oxaliplatin-, and fluoropyrimidine-based combination chemotherapy.

The trial enrolled 1072 subjects who were randomized to receive FOLFIRI plus placebo or FOLFIRI plus ramucirumab. Subjects in the ramucirumab received a dose of 8 mg/kg every 2 weeks until disease progression or unacceptable toxicity occurred. Those in the placebo arm received treatment every 2 weeks. The primary endpoint was overall survival (OS). Subjects who received FOLFIRI plus ramucirumab had a statistically significant difference in OS compared to those who received FOLFIRI plus placebo (HR 0.85; 95% CI: 0.73, 0.98; p=0.023, stratified log-rank test). The median OS was 13.3 and 11.7 months for those in the FOLFIRI plus ramucirumab arm compared to those in the FOLFIRI plus placebo arms, respectively. The median progression free survival was 5.7 months in the FOLFIRI plus ramucirumab group versus 4.5 months in the FOLFIRI plus placebo arm (HR 0.79; 95% CI: 0.70, 0.90; p<0.001). Thyroid dysfunction (hypothyroidism) was reported in 2.6% of participants; however, the safety data was consistent with the known safety profile in the studies of previously approved FDA indications for ramucirumab.

The current NCCN CPGs for colon (V2.2017) and rectal cancer (V2.2017) state there is no data to suggest activity of FOLFIRI plus ramucirumab in an individual who has progressed on FOLFIRI plus bevacizumab, or vice-versa. In addition, ramucirumab has only shown activity in

colorectal cancer when given in conjunction with FOLFIRI in FOLFIRI-naïve individuals. The NCCN CPG also states that ramucirumab should not be used in the adjuvant setting for stage II or III (nonmetastatic) disease outside participation in a clinical trial.

Key Words:

Gastric cancer, Non-small cell lung cancer (NSCLC), colorectal cancer, esophageal adenocarcinoma, Cyramza®, ramucirumab, gastroesophageal junction adenocarcinoma (GEJ)

Approved by Governing Bodies

On April 21, 2014, the FDA approved ramucirumab (Cyramza, Eli Lilly and Company) for use as a single agent for the treatment of individuals with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma (GEJ) with disease progression on or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy.

On November 5, 2014, ramucirumab (Cyramza, Eli Lilly and Company) was approved by the FDA for use in combination with paclitaxel for the treatment of individuals with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma with disease progression during or after treatment with fluoropyrimidine- or platinum-containing chemotherapy.

On December 11, 2014, the FDA approved the use of ramucirumab (Cyramza injection, Eli Lilly and Company) in combination with docetaxel for the treatment of individuals with metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy.

On April 24, 2015, the FDA approved ramucirumab (Cyramza, Eli Lilly and Company) for use in combination with irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) for the treatment of an individual with metastatic colorectal cancer whose disease has progressed on a first line bevacizumab-, oxaliplatin-, and fluoropyrimidine-containing chemotherapy.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT Codes:

J9308	Injection, ramucirumab, 5 mg

References:

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Policy History

New policy created, effective date May 1, 2016.
Medical Policy Group, October 2016: Available for comment October 28, 2016 through December 12, 2016.
Medical Policy Group, October 2017
Medical Policy Group, February 2018
Medical Policy Group, November 2018