**Description**

Ramucirumab (Cyramza®) is an intravenously infused recombinant human monoclonal antibody that is used for the treatment of advanced gastric cancer, gastro-esophageal junction adenocarcinoma, and non-small cell lung cancer (NSCLC) when the disease has progressed after first-line therapy. It works by blocking the formation of blood vessels, thereby preventing the tumor from getting essential nutrients that it needs for growth.
Policy/Criteria

I. Most contracts require prior authorization approval of ramucirumab prior to coverage. Ramucirumab may be considered medically necessary when either criterion A, B, or C below is met:

A. A diagnosis of **metastatic or unresectable, locally advanced gastric cancer** or **esophageal junction (GEJ) adenocarcinoma** when there was disease progression after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy (see Appendix I), or therapy with these regimens was not tolerated or is contraindicated.

OR

B. A diagnosis of squamous or non-squamous **metastatic non-small cell lung cancer (NSCLC)** when criteria 1 and 2 below are met:

1. There has been progression of disease after one prior treatment with a platinum-containing regimen (see Appendix I), unless either criterion a or b below is met:
   a. Documentation of anaplastic lymphoma kinase (ALK) translocation status is provided and, if the NSCLC is ALK-positive, there has been progression of disease following treatment with crizotinib (Xalkori).

   OR

   b. Documentation of an epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) substitution mutation is provided and, if the NSCLC is EGFR mutation positive, there has been progression of disease following treatment with afatinib (Gilotrif) or erlotinib (Tarceva). [refer to Medical Policy, Genetic Testing 56, ‘Molecular Analysis for Targeted Therapy of NSCLC’]

   AND

2. Ramucirumab is given in combination with a taxane (see Appendix I).

OR

C. A diagnosis of **metastatic colorectal cancer** when criteria 1 and 2 below are met:

1. There has been progression of disease on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (See Appendix 2 for example regimens)

   AND

2. Ramucirumab is given in combination with FOLFIRI (leucovorin, fluorouracil, and irinotecan)
II. Administration, Quantity Limitations, and Authorization Period
   A. OmedaRx does not consider ramucirumab to be a self-administered medication.
   B. When prior authorization is approved, ramucirumab may be authorized as follows:
      1. **Gastric cancer, esophageal junction (GEJ) adenocarcinoma and colorectal cancer:** up to 8 mg/kg every two weeks
      2. **Non-small cell lung cancer:** up to 10 mg/kg every 21 days
   C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Ramucirumab is considered investigational when used for all other conditions, including but not limited to:
   A. Brain cancer
   B. Breast cancer
   C. Hepatocellular carcinoma (HCC)
   D. Prostate cancer
   E. Renal cell carcinoma (RCC)

IV. Ramucirumab is considered investigational when used concomitantly with any other targeted therapy, including, but not limited to, afatinib (Gilotri®), bevacizumab (Avastin®), cetuximab (Erbitux®), ceritinib (Zykadia®), gefitinib (Iressa®), nivolumab (Opdivo®), panitumumab (Vectibix®), regorafenib (Stivarga®), or ziv-aflibercept (Zaltrap®).

**Position Statement**

- Ramucirumab, a human IgG1 monoclonal antibody that binds to vascular endothelial growth factor (VEGF) receptors, is approved as a monotherapy or in combination with paclitaxel for the treatment of advanced gastric cancer or advanced gastro-esophageal junction (GEJ) adenocarcinoma after prior treatment with front-line fluoropyrimidine- or platinum-containing chemotherapy.

- Ramucirumab is also approved in combination with docetaxel for the treatment of metastatic non-small cell lung cancer (NSCLC) after prior treatment with front-line platinum-based chemotherapy (with or without maintenance therapy). Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab.

- The third indication for ramucirumab is for the treatment of metastatic colorectal cancer when there has been disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Ramucirumab is given in combination with FOLFIRI.

- In the pivotal clinical trial in patients with locally advanced or metastatic gastric cancer or GEJ adenocarcinoma, a small but statistically significant improvement in overall survival (~ 5.5 weeks) was reported with ramucirumab relative to best supportive care in the second-line, recurrent disease setting.
- In the pivotal clinical trial for NSCLC, a small but statistically significant improvement in overall survival (~5.6 weeks) was reported with ramucirumab in combination with docetaxel relative to placebo in patients who progressed after front-line therapy.
- In the pivotal clinical trials for metastatic colorectal cancer, ramucirumab plus FOLFIRI demonstrated a 1.6 month overall survival advantage compared to placebo plus FOLFIRI in patients who had disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
- There is a lot of interest in studying ramucirumab in many other cancers, such as breast cancer, based on its pharmacology; however, there is currently no published, peer-reviewed evidence that supports clinical benefit in other cancers at this time.
- When used for colorectal cancer, gastric cancer or GEJ, ramucirumab is administered as an intravenous infusion over 60 minutes in a dose of 8 mg/kg given every 2 weeks.
- For NSCLC, ramucirumab is administered on day 1 of a 21-day cycle prior to docetaxel as an intravenous infusion over 60 minutes in a dose of 10 mg/kg.
- Package labeling for ramucirumab includes a boxed warning describing an increased risk of hemorrhage. Death from hemorrhage has been reported.
- Common side effects include hypertension and diarrhea. Infusion reactions may also occur. Premedication with intravenous diphenhydramine is recommended. Dexamethasone and acetaminophen may be added for more severe infusion reactions.

**Clinical Efficacy**

**Advanced Gastric Cancers**

There is moderate certainty in the evidence for ramucirumab with regard to improving overall survival in patients with previously treated, advanced gastric cancers. The body of evidence includes two randomized controlled trials (RCTs): one using ramucirumab as a single agent and one using ramucirumab in combination with chemotherapy.

- A published, randomized, double-blind, placebo controlled trial (REGARD) evaluated the efficacy of ramucirumab relative to placebo in patients with previously treated advanced gastric or gastro-esophageal junction (GEJ) adenocarcinoma. [1]
  * The study enrolled 355 patients who had failed prior therapy with a fluoropyrimidine- or platinum-containing chemotherapy regimen.
  * There was a modest improvement in overall survival in patients receiving ramucirumab versus best supportive care (5.2 months and 3.8 months, respectively).
  * Moderate attrition in the trial lowers the confidence in the results from the trial.
- An unpublished, randomized, double-blind, placebo-controlled trial (RAINBOW) evaluated the efficacy of ramucirumab plus paclitaxel versus paclitaxel alone in patient with previously treated advanced gastric or GEJ adenocarcinoma. [2]
  * The study enrolled 665 patients who had failed prior therapy with a fluoropyrimidine- or platinum-containing chemotherapy regimen.
  * There was a modest improvement in overall survival in patients receiving ramucirumab plus paclitaxel versus those receiving paclitaxel alone (9.6 months and 7.4 months, respectively).
* Moderate attrition and missing details surrounding blinding and concealment of allocation lowers the confidence in the results from the trial.

- There is currently no evidence evaluating the efficacy of ramucirumab in the first-line advanced gastric or GEJ adenocarcinoma setting.

- The National Comprehensive Cancer Network (NCCN) gastric cancer guideline lists ramucirumab as a category 1 option for the second-line treatment of metastatic or locally advanced gastric cancer or GEJ adenocarcinoma when used as monotherapy or in combination with paclitaxel. [3]

**Non-Small Cell Lung Cancer (NSCLC)**

- A published, randomized, double-blind, placebo-controlled trial (REVEL study) evaluated the efficacy of ramucirumab plus docetaxel versus placebo plus docetaxel as second-line therapy in patients with stage IV NSCLC. [4]
  - The study enrolled 1,253 patients whose disease had progressed during or after first-line platinum-based chemotherapy with or without bevacizumab or maintenance therapy.
  - Patients whose only previous therapy for advanced or metastatic disease was EGFR tyrosine kinase inhibitor monotherapy were excluded from the study.
  - There was a modest improvement in overall survival in patients receiving ramucirumab plus docetaxel versus those receiving docetaxel alone (10.5 months and 9.1 months, respectively).

- There is currently no evidence evaluating the efficacy of ramucirumab beyond the second-line setting, or in the first-line setting.

- The NCCN non-small cell lung cancer guideline lists ramucirumab in combination with docetaxel as a category 2A option for metastatic disease in the second-line setting. Patients with ALK rearrangements or sensitizing EGFR mutations are eligible for ramucirumab plus docetaxel if they have progressed after receiving the appropriate targeted therapy. [5]

**Metastatic Colorectal Cancer**

- A published, randomized, double-blind, placebo-controlled trial (RAISE study) evaluated the efficacy of ramucirumab versus placebo in combination with second-line FOLFIRI (leucovorin, fluorouracil, and irinotecan) for metastatic colorectal cancer in patients with disease progression during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. [6]

- The study included 1,072 patients who had disease progression during or within 6 months of the last dose of first-line therapy. The primary endpoint was overall survival (OS).

- Median OS was 13.3 months (95% CI 12.4 – 14.5) for ramucirumab-treated patients compared to 11.7 months (95% CI 10.8 – 12.7) for placebo-treated patients. However, the clinical significance of a 1.6 month survival advantage in colorectal cancer is uncertain.

- The NCCN colon cancer and rectal cancer guidelines include ramucirumab in combination with FOLFIRI as a category 2A recommendation for therapy after first progression. Bevacizumab plus FOLFIRI is the preferred option in this setting. [7,8]
Other Cancer Settings and Conditions

- There are ongoing clinical trials designed to evaluate the efficacy of ramucirumab in brain cancer, prostate cancer, and renal cell carcinoma; however, there is currently no clinical evidence to support its use in these conditions. [9]

- In a phase III study in patients with human epidermal growth factor receptor 2 (HER2)-negative, unresectable, locally recurrent or metastatic breast cancer, the addition of ramucirumab to docetaxel failed to improve overall survival over docetaxel alone. [9]

- In a phase III study (REACH) in 565 patients with previously treated hepatocellular carcinoma, treatment with second-line ramucirumab failed to improve overall survival over best supportive care. [10]

OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN clinical practice guidelines.

Safety [11]

- Package labeling for ramucirumab includes a boxed warning describing an increased risk of hemorrhagic events with ramucirumab. Some cases have resulted in death.

- The most common adverse events reported with ramucirumab as a single agent include hypertension and diarrhea.

- The most common adverse reactions reported with ramucirumab plus paclitaxel include fatigue, neutropenia, diarrhea, and epistaxis. When used in combination with docetaxel, the most common adverse reactions reported include neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation.

- Infusion-related reactions are also possible. Premedication with diphenhydramine is recommended. For more severe reactions, dexamethasone and acetaminophen may be used.

- Similar to other VEGF inhibitors, ramucirumab may cause gastrointestinal perforation, impaired wound healing, and clinical deterioration in patients with cirrhosis.

Dosing considerations [11]

- The recommended dose of ramucirumab for gastric cancer, esophageal junction adenocarcinoma, and metastatic colorectal cancer is 8 mg/kg intravenously every two weeks.

- For NSCLC, the recommended dose of ramucirumab is 10 mg/kg intravenously on day 1 of a 21-day cycle prior to docetaxel infusion.

- The infusion rate should be decreased by 50% if grade 1 or 2 infusion reactions occur. Ramucirumab should be permanently discontinued for grade 3 or 4 infusion-related reactions.
Appendix 1: Platinum, Taxane and Fluoropyrimidine Medications

<table>
<thead>
<tr>
<th>Platinum medications</th>
<th>Fluoropyrimidine medications</th>
<th>Taxane medications</th>
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</thead>
<tbody>
<tr>
<td>cisplatin</td>
<td>capecitabine (Xeloda®)</td>
<td>cabazitaxel (Jevtana®)</td>
</tr>
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<td>floxuridine</td>
<td>docetaxel</td>
</tr>
<tr>
<td>oxaliplatin (Eloxatin®)</td>
<td>fluorouracil (5-FU, Adrucil®)</td>
<td>paclitaxel nab-paclitaxel (Abraxane®)</td>
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</tbody>
</table>

Appendix 2: Example Chemotherapy Regimens for Metastatic Colorectal Cancer Containing bevacizumab, oxaliplatin, and a fluoropyrimidine [7,8]

<table>
<thead>
<tr>
<th>Regimen Name</th>
<th>Included Medications</th>
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<tbody>
<tr>
<td>mFOLFOX6 + bevacizumab</td>
<td>oxaliplatin, leucovorin, fluorouracil (5-FU), bevacizumab</td>
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<tr>
<td>CapeOx + bevacizumab</td>
<td>oxaliplatin, capecitabine, bevacizumab</td>
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<tr>
<td>FOLFIRI + bevacizumab</td>
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Cross References

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<td>Zykadia™, ceritinib</td>
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<td>dru354</td>
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Codes

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<tr>
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<td>J3490</td>
<td>Unclassified drugs</td>
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<td>ICD-9</td>
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<td>ICD-10</td>
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<td>Esophageal and Esophagogastric Junction Cancers</td>
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References


