Clinical Policy: Ramucirumab (Cyramza)
Reference Number: CP. PHAR.119
Effective Date: 06.01.15
Last Review Date: 02.20
Line of Business: Medicaid, HIM-Medical Benefit

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Ramucirumab (Cyramza®) is an anti-vascular endothelial growth factor antibody.

FDA Approved Indication(s)
Cyramza is indicated:
- As a single agent or in combination with paclitaxel, for treatment of advanced gastric or gastro-esophageal junction (i.e., esophagogastric junction; EGJ) adenocarcinoma, with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.
- In combination with docetaxel, for treatment of metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Cyramza.
- In combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), for the treatment of metastatic colorectal cancer (CRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
- As a single agent, for the treatment of hepatocellular carcinoma (HCC) in patients who have an alpha fetoprotein of ≥ 400 ng/mL and have been treated with sorafenib.

Policy/Criteria
Provider must submit documentation (including such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Cyramza is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Esophageal, Esophagogastric Junction, and Gastric Cancer (must meet all):
      1. Diagnosis of advanced esophageal, EGJ or gastric cancer;
      2. Prescribed by or in consultation with an oncologist;
      3. Age ≥ 18 years;
      4. Prescribed as subsequent therapy either as a single agent or in combination with paclitaxel;
      5. Request meets one of the following (a or b):*
         a. Dose does not exceed 8 mg per kg every 2 weeks;
         b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   *Prescribed regimen must be FDA-approved or recommended by NCCN
Approval duration: 6 months

B. Non-Small Cell Lung Cancer (must meet all):
1. Diagnosis of metastatic NSCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as subsequent therapy in combination with docetaxel;
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 10 mg per kg on day 1 of a 21-day cycle;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
*Prescribed regimen must be FDA-approved or recommended by NCCN

Approval duration: 6 months

C. Colorectal Cancer (must meet all):
1. Diagnosis of metastatic CRC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as subsequent therapy in combination with irinotecan or FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil);
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 8 mg per kg every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
*Prescribed regimen must be FDA-approved or recommended by NCCN

Approval duration: 6 months

D. Hepatocellular Carcinoma (must meet all):
1. Diagnosis of HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. α-fetoprotein (AFP) ≥ 400 ng/mL;
5. Disease has progressed on or after therapy with Nexavar®;
   *Prior authorization is required for Nexavar
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 8 mg per kg every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
*Prescribed regimen must be FDA-approved or recommended by NCCN

Approval duration: 6 months

E. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid and HIM-Medical Benefit
II. Continued Therapy

A. All Indications in Section I (must meet all):
   1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Cyramza for a covered indication and has received this medication for at least 30 days;
   2. Member is responding positively to therapy;
   3. If request is for a dose increase, request meets one of the following (a, b, or c):
      a. Esophageal/EGJ/gastric cancer, CRC, HCC: New dose does not exceed 8 mg per kg every 2 weeks;
      b. NSCLC: New dose does not exceed 10 mg per kg on day 1 of a 21-day cycle;
      c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

   Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
      Approval duration: Duration of request or 6 months (whichever is less); or
   2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid and HIM-Medical Benefit.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – CP.PMN.53 for Medicaid and HIM-Medical Benefit, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

- AFP: α-fetoprotein
- CRC: colorectal carcinoma
- EGJ: esophagogastric junction
- FDA: Food and Drug Administration
- HCC: Hepatocellular Carcinoma
- FOLFIRI: fluorouracil, leucovorin, irinotecan
- NSCLC: non-small cell lung cancer

Appendix B: Therapeutic Alternatives

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>paclitaxel</td>
<td>Esophageal, EGF, or gastric cancer: Varies</td>
<td>Varies</td>
</tr>
<tr>
<td>docetaxel (Taxotere®)</td>
<td>NSCLC: Varies</td>
<td>Varies</td>
</tr>
<tr>
<td>irinotecan (Camptosar®)</td>
<td>CRC: Varies</td>
<td>Varies</td>
</tr>
<tr>
<td>FOLFIRI (5-FU, leucovorin, irinotecan)</td>
<td>CRC: Varies</td>
<td>Varies</td>
</tr>
</tbody>
</table>
Appendix C: Contraindications/BoxedWarnings
None reported

Appendix D: General Information

- Hepatocellular carcinoma: Serum levels of alpha-fetoprotein (AFP) are typically higher for advanced HCC compared to early HCC, but overall, levels do not correlate well with clinical features of HCC, such as tumor size or vascular invasion. Not all tumors secrete AFP. The biomarker at concentrations higher than 400 ng/mL is associated with poor prognosis. After treatment with sorafenib, half the patients express alpha-fetoprotein concentrations greater than 400 ng/mL. In the pivotal trial (REACH-2), both Cyramza and placebo groups had baseline alpha-fetoprotein labs greater than 400 ng/mL. While there is debate regarding sensitivity and specificity of this biomarker, the criteria for AFP ≥ 400 ng/mL is consistent with both FDA-approved labeling and NCCN guideline recommendations.

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric or EGJ adenocarcinoma</td>
<td>8 mg/kg every 2 weeks administered as an intravenous infusion over 60 minutes.</td>
<td>8 mg/kg</td>
</tr>
<tr>
<td>NSCLC</td>
<td>10 mg/kg administered by intravenous infusion over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion.</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>CRC</td>
<td>8 mg/kg every 2 weeks administered by intravenous infusion over 60 minutes prior to FOLFIRI administration.</td>
<td>8 mg/kg</td>
</tr>
<tr>
<td>HCC</td>
<td>8 mg/kg every 2 weeks administered as an intravenous infusion over 60 minutes.</td>
<td>8 mg/kg</td>
</tr>
</tbody>
</table>

VI. Product Availability

Single-dose vial: 100 mg/10 mL (10 mg/mL) solution, 500mg/50mL (10mg/mL) solution

VII. References

CLINICAL POLICY
Ramucirumab


Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>J9308</td>
<td>Injection, ramucirumab, 5mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reviews, Revisions, and Approvals
Policy developed. 05.01.15 05.15
Policy converted to new template. 04.01.16 05.16
Gastric cancer: removed requirement of failing a fluoropyrimidine- or platinum-containing chemotherapy; edited to allow approval if disease progress on/after prior chemotherapy per NCCN.
NSCLC: removed requirement of failure of platinum-based chemotherapy, simplified language to include appropriate treatment regarding ALK and EGFR aberration status.
Colorectal cancer: changed requirement for the use of bevacizumab, oxaliplatin, and a fluoropyrimidine to a prior regimen containing bevacizumab per NCCN. Changed requirement of concurrent use with FOLFIRI to irinotecan containing regimen instead per NCCN; changed initial approval duration to 3 months; added impaired wound healing to reasons to discontinue per PI boxed warning.
Esophageal cancer added to section A. Lung cancer notations of specific required prior therapy are removed. Colorectal cancer indications updated around FDA and NCCN uses. Safety criteria removed as there are no contraindications or black box warnings precluding treatment.
**CLINICAL POLICY**

**Ramucirumab**

**Reviews, Revisions, and Approvals**

<table>
<thead>
<tr>
<th>Description</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changed initial approval duration to 6 months. Changed continued approval to 12 months.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1Q18 annual review: - Age, dosing, specialist added. - NCCN recommendations removed for lung and colon cancer. - References reviewed and updated.</td>
<td>12.01.17</td>
<td>02.18</td>
</tr>
<tr>
<td>1Q 2019 annual review; HIM-Medical Benefit line of business added; NCCN and FDA-approved uses summarized for improved clarity - progression on specific therapies removed across indications; for CRC combination therapy with irinotecan is added; references reviewed and updated.</td>
<td>11.13.18</td>
<td>02.19</td>
</tr>
<tr>
<td>RT4: Criteria added for new FDA indication as a single-agent therapy for the treatment of advanced HCC; removed BBW based on updated prescribing information; references reviewed and updated.</td>
<td>07.05.19</td>
<td></td>
</tr>
<tr>
<td>1Q 2020 annual review: no significant changes; references reviewed and updated.</td>
<td>10.31.19</td>
<td>02.20</td>
</tr>
</tbody>
</table>

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or
regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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**Note: For Medicaid members,** when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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