OVERVIEW
Cyramza, a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist, is approved for the following indications:¹

1) Gastric or gastroesophageal (GE) junction adenocarcinoma, as a single agent or in combination with paclitaxel injection for the treatment of patients with advanced or metastatic disease with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy;

2) Metastatic non-small cell lung cancer (NSCLC), in combination with docetaxel intravenous injection (Docefrez™, Taxotere®, generics) for the treatment of patients with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Cyramza.

3) Metastatic colorectal cancer (mCRC), in combination with FOLFIRI (irinotecan, leucovorin, and 5-fluorouracil [5-FU]) for the treatment of patients with disease progression on or after prior therapy with Avastin® (bevacizumab intravenous injection), oxaliplatin, and a fluoropyrimidine.

4) Hepatocellular carcinoma (HCC), as a single agent in patients who have an alpha fetoprotein of ≥ 400 ng/mL and have been treated with sorafenib.

Guidelines
The National Comprehensive Cancer Network (NCCN) guidelines on colon cancer (version 2.2019 – May 15, 2019) and rectal cancer (version 2.2019 – May 30, 2019) recommend Cyramza as primary therapy and subsequent therapy for patients with unresectable advanced or metastatic disease in combination with either irinotecan or FOLFIRI.²⁻⁴ The NCCN guidelines on gastric cancer (version 1.2019 – March 14, 2019) and esophageal and esophagogastric junction cancers (version 2.2019 – May 29, 2019) recommend Cyramza as palliative treatment for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease.⁴⁻⁶ The NCCN guidelines on NSCLC (version 4.2019 – April 29, 2019) recommend Cyramza as subsequent therapy in combination with docetaxel for metastatic disease for patients who have not previously received docetaxel either following progression on initial cytotoxic therapy or for further progression on a systemic immune checkpoint inhibitor or other systemic therapy.⁴⁻⁷ The NCCN guidelines for hepatobiliary cancers (version 2.2019 – March 6, 2019) recommends Cyramza as a single agent for the treatment of patients with progressive disease with an alpha fetoprotein ≥ 400 ng/mL.⁴⁻⁸

POLICY STATEMENT
Prior authorization is recommended for medical benefit coverage of Cyramza. Approval is recommended for those who meet the Criteria and Dosing for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Cyramza as well as the monitoring required for adverse events and long-term efficacy, approval requires Cyramza to be prescribed by or in consultation with a physician who specializes in the condition being treated.
RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Cyramza is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Colon or Rectal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
   A) Cyramza is prescribed by or in consultation with an oncologist; AND
   B) The patient has received oxaliplatin, and a fluoropyrimidine (e.g., 5-fluorouracil [5-FU], capecitabine); AND
   C) Cyramza will be used in combination with irinotecan or with FOLFIRI (irinotecan, folinic acid [leucovorin], and 5-fluorouracil [5-FU]).

   Dosing. Approve the following dosing regimen: Up to 8 mg/kg as an intravenous infusion administered no more frequently than once every 2 weeks.

   The recommended dose is 8 mg/kg every 2 weeks given as an intravenous infusion over 60 minutes prior to FOLFIRI administration.\(^1\) Cyramza is continued until disease progression or unacceptable toxicity. Dose modifications are recommended in the prescribing information for infusion-related reactions, hypertension, proteinuria, arterial thromboembolic events, gastrointestinal perforation, or Grade 3 or 4 bleeding. Therapy with Cyramza is interrupted before scheduled surgery until the wound is fully healed. Management of AEs may require that Cyramza be withheld or permanently discontinued as determined by the prescribing physician.

2. Gastric, Esophagogastric Junction, or Esophageal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
   A) Cyramza is prescribed by or in consultation with an oncologist; AND
   B) Cyramza will be used alone or in combination with paclitaxel; AND
   C) The patient has received chemotherapy with at least ONE of the following (i or ii):
      i. 5-Fluorouracil (5-FU) or capecitabine; OR
      ii. Cisplatin, carboplatin, or oxaliplatin.

   Dosing. Approve the following dosing regimen: Up to 8 mg/kg as an intravenous infusion administered no more frequently than once every 2 weeks.

   The recommended dose, either as a single agent or in combination with weekly paclitaxel, is 8 mg/kg every 2 weeks given as an intravenous infusion over 60 minutes.\(^1\) Cyramza is continued until disease progression or unacceptable toxicity. When used in combination, Cyramza is given before administering paclitaxel. Dose modifications are recommended in the prescribing information for infusion-related reactions, hypertension, proteinuria, arterial thromboembolic events, gastrointestinal perforation, or Grade 3 or 4 bleeding. Therapy with Cyramza is interrupted before scheduled surgery until the wound is fully healed. Management of AEs may require that Cyramza be withheld or permanently discontinued as determined by the prescribing physician.

3. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   A) Cyramza is prescribed by or in consultation with an oncologist; AND
B) Cyramza will be used in combination with docetaxel intravenous injection (Docfrez™, Taxotere®, generics); AND
C) The patient has tried a platinum-based chemotherapy (e.g., cisplatin, carboplatin); AND
D) The patient has one of the following histologic subtypes of NSCLC (i or ii):
   i. Non-squamous cell carcinoma (that is, adenocarcinoma, large cell, or NSCLC not otherwise specified) AND one of the following conditions is met (a or b):
      a) The patient’s tumor is positive for a targetable mutation (i.e., sensitizing epidermal growth factor \[EGFR\] mutation, anaplastic lymphoma kinase \[ALK\] fusions) AND the patient has received targeted drug therapy for the specific mutation; OR
      b) The tumor is negative or unknown for these targetable mutations (i.e., \[EGFR\], \[ALK\]); OR
   ii. Squamous cell carcinoma.

Dosing. Approve the following dosing regimen: Up to 10 mg/kg as an intravenous infusion no more frequently than once every 3 weeks.

The approved dosing of Cyramza in NSCLC is 10 mg/kg given intravenously over about 60 minutes on Day 1 of a 21-day cycle prior to infusion of docetaxel.\(^1\) Cyramza is continued until disease progression or unacceptable toxicity. Dose modifications are recommended in the prescribing information for infusion-related reactions, hypertension, proteinuria, arterial thromboembolic events, gastrointestinal perforation, or Grade 3 or 4 bleeding. Therapy with Cyramza is interrupted before scheduled surgery until the wound is fully healed. Management of AEs may require that Cyramza be withheld or permanently discontinued as determined by the prescribing physician.

4. **Hepatocellular Carcinoma.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   A) Cyramza is prescribed by or in consultation with an oncologist; AND
   B) The patient has been treated with Nexavar® (sorafenib tablet); AND
   C) Cyramza will be used as a single agent; AND
   D) The patient has an alpha fetoprotein of \(\geq 400\) ng/mL.

Dosing. Approve the following dosing regimen: Up to 8 mg/kg as an intravenous infusion administered no more frequently than once every 14 days.

The approved dosing of Cyramza in hepatocellular carcinoma is 8 mg/kg given intravenously over about 60 minutes on Day 1 of a 14-day cycle.\(^1\) Cyramza is continued until disease progression or unacceptable toxicity. Dose modifications are recommended in the prescribing information for infusion-related reactions, hypertension, proteinuria, arterial thromboembolic events, gastrointestinal perforation, or Grade 3 or 4 bleeding. Therapy with Cyramza is interrupted before scheduled surgery until the wound is fully healed. Management of AEs may require that Cyramza be withheld or permanently discontinued as determined by the prescribing physician.

5. **Other Cancer-Related Indications.** Forward to the Medical Director for review on a case-by-case basis.

**CONDITIONS NOT RECOMMENDED FOR APPROVAL**
Cyramza has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES


OTHER REFERENCES UTILIZED


<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual</td>
<td>Esophageal cancer indication was added to criteria for gastric or gastroesophageal junction cancer. Criteria for NSCLC (non-squamous cell) were revised to add that testing for <em>EGFR T790M</em> mutation and for <em>ROS1</em> rearrangements is required and prior targeted therapy is required if appropriate. Detection of <em>EGFR</em> mutations, <em>EGFR T790M</em> mutation, <em>ALK</em> fusions, or <em>ROS1</em> rearrangements is necessary for selection of patients appropriate for targeted therapies before using Cyramza.</td>
<td>05/04/2016</td>
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<tr>
<td>Annual</td>
<td>Criteria for NSCLC were revised.</td>
<td>05/17/2017</td>
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<tr>
<td>Annual</td>
<td>• NSCLC: Criteria were divided into non-squamous cell and squamous cell histologies. For non-squamous cell histologies, the list of targeted therapies used for each aberration was removed; testing for both <em>EGFR</em> and <em>ALK</em> is required; testing for <em>ROS1</em> was removed; <em>EGFR</em> and <em>ALK</em> are negative was added as an option after testing. In Labs/Diagnostics, testing for <em>ROS1</em> rearrangements was removed.</td>
<td>06/27/2018</td>
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<tr>
<td>Annual</td>
<td>Colon or rectal cancer. Changed name to Colon or Rectal Cancer. Removed advanced or metastatic colorectal cancer that has progressed on or after therapy with Avastin from 1B and added in combination with irinotecan to 1C. Gastric, Esophagogastroduodenal Junction, or Esophageal Cancer. Removed locally advanced or metastatic disease criteria from policy. Non-Small Cell Lung Cancer. Removed advanced or metastatic disease criteria from policy. Reworded criteria regarding the use of applicable targetable mutation therapies to be in line with other oncology policies. Hepatocellular carcinoma. Added approval criteria for hepatocellular carcinoma. Approval duration. Increased approval duration to 1 year for all indications. Conditions Not Recommended For Approval. Removed breast cancer from the Conditions Not Recommended For Approval section. Removed Patient has been Started on Cyramza and Waste Management for All Indications sections.</td>
<td>06/12/2019</td>
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