Department:	Pharmacy Management	**Original Approval:**	12/24/2015
Policy #:	PM112	**Last Approval:**	09/12/2019
Title:	Ramucirumab (Cyramza®)		
Approved By:	UM Pharmacy Subcommittee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Ramucirumab (Cyramza): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Prescribed by or in consultation with an oncologist - Medication list (current and past) to include start and end dates of all chemotherapy regimens -Dosing and duration requested - Weight -Age -Labs/diagnostics as indicated.

BACKGROUND

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]

Cyramza is available as preservative-free, solution at a concentration of 10 mg/mL in either 100 mg or 500 mg single-dose vials.[1] The calculated dose is further diluted with 0.9% Sodium Chloride Injection in an intravenous infusion container to a final volume of 250 mL. The diluted Cyramza is given over 60 minutes intravenously. Prior to each Cyramza infusion, the patient is premedicated with an intravenous histamine H1 antagonist (e.g., diphenhydramine). Patients who experience Grade 1 or 2 infusion-related reactions, are also premedicated with dexamethasone (or equivalent) and acetaminophen before each Cyramza dose.

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

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):

Criteria. *The patient must meet 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 in mCRC in Adults.
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.

Criteria. 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 in Gastric, Esophagogastric Junction, or Esophageal Cancer in Adults. *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 (NSCLC).

Criteria. *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 (Docefrez™, 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):
    (1) 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

(2) The tumor is negative or unknown for these targetable mutations (i.e., *EGFR, ALK*); OR

ii. Squamous cell carcinoma.

Dosing in NSCLC in Adults. *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.

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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 ≥ 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.

Waste Management for All Indications.
Dosing for Cyramza is based on body weight (mg/kg). The dose should be calculated and the number of vials needed assessed.

Conditions Not Recommended for Approval

1. 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

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

SPECIAL CONSIDERATIONS

None.

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

References	1. Cyramza® injection for intravenous use [prescribing information]. Indianapolis, IN: Eli Lilly and Company; March 2017. 2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – May 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 30, 2019. 3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – May 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 30, 2019. 4. The NCCN Drugs & Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 30, 2019. Search term: ramucirumab. 5. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (Version 1.2019 - March 14, 2019). © 2019 National

Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 31, 2019.
6. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (Version 2.2019 – May 29, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 31, 2019.
7. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – April 29, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 31, 2019.
8. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (Version 2.2019 – March 6, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 31, 2019.

Other References Utilized

- Tabernero J, Yoshino T, Cohn AL, et al; RAISE Study Investigators. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol*. 2015;16:499-508.
- Fuchs CS, Tomasek J, Yong CJ, et al; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2014;383:31-39.
- Wilke H, Muro K, Van Cutsem E, et al; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol*. 2014;15:1224-1235.
- Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384:665-673.
- Mackey JR, Ramos-Vazquez M, Lipatov O, et al. Primary results of ROSE/TRIO-12, a randomized placebo-controlled phase III trial

	evaluating the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer. *J Clin Oncol*. 2015;33:141-148. • Petrylak DP, Tagawa ST, Kohli M, et al. Docetaxel as monotherapy or combined with ramucirumab or icrucumab in second-line treatment for locally advanced or metastatic urothelial carcinoma: An open-label, three-arm, randomized controlled phase II trial. *J Clin Oncol*. 2016;34:1500-1509. • Park K, Kim JH, Cho EK, et al. East Asian subgroup analysis of a randomized, double-blind, phase 3 study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small cell lung cancer following disease progression after one prior platinum-based therapy (REVEL). *Cancer Res Treat*. 2016;48(4):1177-1186. • Yardley DA, Reeves J, Dees EC, et al. Ramucirumab with eribulin versus eribulin in locally recurrent or metastatic breast cancer previously treated with anthracycline and taxane therapy: A multicenter, randomized, phase II study. *Clin Breast Cancer*. 2016;16(6):471-479. • Petrylak DP, de Wit R, Chi KN, et al; RANGE study investigators. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial. *Lancet*. 2017;390(10109):2266-2277. • Chau I, Peck-Radosavljevic M, Borg C, et al. Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib: Patient-focused outcome results from the randomised phase III REACH study. *Eur J Cancer*. 2017;81:17-25. • Zhu AX, Kang Y-K, Yen C-J, et al. REACH-2: A randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib [abstract]. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; Chicago, IL; June 1-5. Available at: https://meetinglibrary.asco.org/record/159169/abstract. Accessed on June 25, 2018.
CFR	42 CFR § 438.210
WAC	WAC 284-43-2050
RCW	

Contract Citation	☒ WAH	AH section 17.3.2.1 General Description of Contracted Services - Pharmacy Benefit and Services - Apple Health Preferred Drug List and Plan Formularies
	☒ IMC	IMC section 16.12.2 General Description of Contracted Services - Pharmacy Benefit and Services - Apple Health Preferred Drug List and Plan Formularies
	☐ MA	
Other Requirements		
NCQA Elements		

Revision History

Revision Date	Revision Description	Revision Made By
12/23/2015	New	Kelly Force; Yusuf Rashid, RPh
12/24/2015	Approval	MMLT
01/11/2017	No revisions	Fran McGaugh
01/12/2017	Approval	MMLT
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/09/2018	Reassigned from UM to PM	Cindy Bush
04/25/2018	Transferred to new template	Cindy Bush
05/23/2018	No revisions	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee
08/09/2018	Annual revision: For NSCLC, section divided into non-squamous and squamous. Non-squamous requires testing for mutations for EGFR and ALK for approval	Jennifer Farley, PharmD
09/19/2018	Approval	UM Committee
08/15/2019	Annual revision: New indication for hepatocellular carcinoma. Change from colorectal cancer to colon or rectal cancer. For gastric, esophageal, and nsclc, removed requirement that it must be advanced or metastatic. Changed duration of approval to 1 yr.	Jennifer Farley, PharmD
09/12/2019	Approval	UM Pharmacy Subcommittee