Department:	Pharmacy Management	**Original Approval:**	01/13/2016
Policy #:	PM133	**Last Approval:**	06/14/2018
Title:	Ziv-aflibercept (Zaltrap®)		
Approved By:	UM Committee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Ziv-aflibercept (Zaltrap): 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 agents -Dosing and duration requested -Weight.

BACKGROUND

Zaltrap, in combination with FOLFIRI (5-fluorouracil [5-FU], leucovorin, and irinotecan), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.[1] Zaltrap is a recombinant fusion protein consisting of vascular endothelial growth factor (VEGF) receptors 1 and 2 fused to the Fc portion of the human immunoglobulin G1 (IgG1). Zaltrap acts as a soluble receptor that binds to human VEGF-A, VEGF- B, and placental growth factor (PIGF). By binding to these endogenous ligands, Zaltrap can inhibit the binding and activation of their cognate receptors, resulting in decreased neovascularization and decreased vascular permeability.

Zaltrap is available in single-use 5 mL and 10 mL vials at a concentration of 25 mg/mL (100 mg/4 mL or 200 mg/8 mL). Zaltrap should be diluted in 0.9% sodium chloride injection or 5% dextrose solution to achieve a final concentration of 0.6 to 8 mg/mL. The diluted solution is administered as an intravenous infusion over 1 hour.

DEFINITIONS

None.

INDICATIONS/CRITERIA

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

Coverage of Zaltrap is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Colorectal Cancer.

Criteria. *Patient must meet the following criteria (A, B, C, D, AND E)*:

- **A)** Zaltrap is prescribed by or in consultation with an oncologist; AND
- **B)** Patient has advanced or metastatic disease; AND
- **C)** Patient has disease that is resistant to or has progressed following an oxaliplatin- or fluoropyrimidine- (5-fluorouracil [5-FU], capecitabine [Xeloda® tablets, generics]) containing regimen; AND
- **D)** The patient has not previously been treated with FOLFIRI (5-fluorouracil [5-FU], leucovorin, and irinotecan); AND
- **E)** Zaltrap will be used in combination with 5-fluorouracil (5-FU) or capecitabine and/or irinotecan.

Preferred Drug. The patient is required to try Avastin® (bevacizumab solution for intravenous infusion), or was intolerant to Avastin.

Avastin is indicated for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-FU-based chemotherapy.[2] Avastin, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with mCRC who have progressed on a first-line Avastin-containing regimen.

The National Comprehensive Cancer Network (NCCN) colon cancer guidelines (version 2.2017)[3] and rectal cancer guidelines (version 3.2017)[4] recommend Zaltrap as 1) primary treatment for patients with unresectable metachronous metastases and previous adjuvant FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) regimens within the past 12 months in combination with irinotecan OR with FOLFIRI, or 2) subsequent therapy after first progression of unresectable advanced or metastatic disease in combination with irinotecan or with FOLFIRI for disease not previously treated with an irinotecan-based regimen. Both of these uses have a category 2A recommendation. In patients with advanced or metastatic disease, Zaltrap is not listed as an option for initial therapy. Zaltrap should not be used as adjuvant therapy for patients with Stage III or IV colon cancer outside of a clinical trial.

Zaltrap has only been effective when given with FOLFIRI in FOLFIRI naïve patients.[3-4] There are no data suggesting activity of Zaltrap plus FOLFIRI in patients who progressed on FOLFIRI plus Avastin or vice versa. No data suggest that single-agent Zaltrap has therapeutic activity. The NCCN panel includes Zaltrap as a second-line option in combination with FOLFIRI or irinotecan only after progression on therapy that does not include irinotecan. The NCCN panel prefers Avastin over Zaltrap and Cyramza as an anti-angiogenic agent based on toxicity and cost.

In one Phase III double-blind, pivotal trial (VELOUR), patients with mCRC who were resistant to or who had progressed during or within 6 months of receiving oxaliplatin-based chemotherapy with or without

Avastin were randomized to Zaltrap 4 mg/kg as an intravenous infusion plus FOLFIRI (n = 612) or to placebo plus FOLFIRI (n = 614) every 2 weeks.[1,5] Treatment cycles were continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was overall survival (OS). Median OS was 12.06 months (95% confidence interval [CI]: 11.07, 13.08) in patients who received placebo/FOLFIRI and 13.50 months (95% CI: 12.52, 14.95) in patients on Zaltrap/FOLFIRI (hazard ratio 0.817; 95% CI: 0.714, 0.935; P = 0.0032). Median progression-free survival was 4.67 months (95% CI: 4.21, 5.36) in patients on placebo/FOLFIRI and 6.9 months (95% CI: 6.51, 7.20) in patients on Zaltrap/FOLFIRI. In a subgroup analysis from the VELOUR trial, patients with prior Avastin therapy who received Zaltrap had a median OS of 12.5 months (95% CI: 10.8, 15.5) vs. 11.7 months (95% CI: 9.8, 13.8) in patients who received placebo.[3] In patients with no prior Avastin use, the median OS was 13.9 months vs. 12.4 months, respectively for Zaltrap vs. placebo.

Dosing in Metastatic Colorectal Cancer. *Dosing must meet ONE of the following (A OR B):*

- **A)** 4 mg per kg intravenous infusion every 2 weeks;[1,3-4] OR
- **B)** 2 mg per kg intravenous infusion every 2 weeks.[1]

The approved dose of Zaltrap is 4 mg/kg as an intravenous infusion given over 1 hour every 2 weeks.[1] Zaltrap is continued until disease progression or unacceptable toxicity. Zaltrap should be temporarily suspended for recurrent or severe hypertension or for recurrent proteinuria. When resuming Zaltrap after these adverse effects are controlled, the dose should be permanently reduced to 2 mg/kg.

Note: Administer Zaltrap prior to any component of the FOLFIRI regimen on the day of treatment.[1] Temporarily suspend Zaltrap at least 4 weeks prior to elective surgery, for recurrent or severe hypertension, and for proteinuria of 2 grams/24 hours. See the prescribing information for more detail.

Initial Approval/Extended Approval.

- **A)** *Initial Approval:* Approve 6 months of therapy.
- **B)** *Extended Approval:* Approve at additional 6-month intervals if the patient does not have disease progression, as determined by the prescribing physician.

Duration of Therapy in Metastatic Colorectal Cancer. Indefinite if the patient does not have disease progression, as determined by the prescribing physician.

Labs/Diagnostics. None required.

Other Uses with Supportive Evidence

2. **Patient has been Started on Zaltrap.** Approve if the patient meets the conditions for coverage required for **Dosing**, **Extended Approval**, **Duration of Therapy**, and **Labs/Diagnostics** for an approved use in this *Zaltrap Utilization Review* policy.

3. **Other Cancer Indications.** Forward to the Medical Director for review on a case-by-case basis. The *NCCN Compendium* only includes recommendations for use of Zaltrap in colon and/or rectal cancer.[6]

Waste Management for All Indications.
Weight-based dosing is used; the dose should be calculated and the number of vials needed assessed.

Conditions Not Recommended for Approval
Other Indications (Non-Cancer). Coverage is not recommended for circumstances not listed in the Authorization Criteria (FDA-approved indications and Other Uses with Supportive Evidence). 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. Zaltrap® injection for intravenous infusion [prescribing information]. Bridgewater, NJ: Regeneron Pharmaceutical, Inc./sanofi-aventis U.S. LLC; June 2016. 2. Avastin® solution for intravenous infusion [prescribing information]. South San Francisco, CA: Genentech, Inc.; December 2016. 3. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 2.2017 – March 13, 2017). © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 17, 2017. 4. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 3.2017 – March 13, 2017). © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 17, 2017. 5. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III

	randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol*. 2012;30:3499-3506. 6. The NCCN Drugs and Biologics Compendium. © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 9, 2017. Search term: ziv-aflibercept. **OTHER REFERENCES UTILIZED** • Ruff P, Ferry DR, Lakomỳ R, et al. Time course of safety and efficacy of aflibercept in combination with FOLFIRI in patients with metastatic colorectal cancer who progressed on previous oxaliplatin-based therapy. *Eur J Cancer*. 2015;51:18-26. • Tabernero J, Van Cutsem E, Lakomý R, et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. *Eur J Cancer*. 2014;50:320-331. • Folprecht G, Pericay C, Saunders MP, et al. Oxaliplatin and 5-FU/folinic acid (modified FOLFOX6) with or without aflibercept in first-line treatment of patients with metastatic colorectal cancer: the AFFIRM study. *Ann Oncol*. 2016;27(7):1273-1279.
CFR	
WAC	WAC 284-43-2050
RCW	
Contract Citation	☒ WAH ☒ IMC ☒ MA
Other Requirements	
NCQA Elements	

Revision History

Revision Date	Revision Description	Revision Made By
01/13/2016	New	Kelly Force; Yusuf Rashid, RPh
01/20/2016	Approval	MMLT
02/24/2017	Title (corrected spelling of medication name)	Sophia Yun, PharmD
02/28/2017	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 UM145 to PM133	Cindy Bush
05/03/2018	Transferred to new template	Cindy Bush
5/21/2018	Selected Revisions	Gary Deng, Pharmacy Student Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee