MEDICAL MUTUAL®

MedicalPolicy

Policy:	**201517- CC**	**Initial Effective Date: 07/30/2015**
Code(s):	**HCPCS J9400**	**Annual Review Date: 04/19/2018**
SUBJECT:	Zaltrap® (ziv-aflibercept injection for intravenous infusion)	**Last Revised Date: 04/19/2018**

Prior approval is required for some or all procedure codes listed in this Corporate Medical.

OVERVIEW

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.

POLICY STATEMENT

This policy involves the use of Zaltrap. Prior authorization is recommended for medical benefit coverage of Zaltrap. Approval is recommended for those who meet the conditions of coverage in the **Criteria**, **Preferred Drug (when applicable), Dosing**, **Initial or Extended Approval**, **Duration of Therapy**, and **Labs/Diagnostics** required for the diagnosis provided. The requirement that the patient meet the Criteria and Preferred Drug for coverage of the requested medication applies to the initial authorization only. **Waste Management** applies for all covered conditions. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria and Waste Management section.

Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Zaltrap, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Zaltrap to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy.

RECOMMENDED AUTHORIZATION CRITERIA

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.

Zaltrap, in combination with FOLFIRI, is indicated for patients with mCRC that is resistant to or has progressed following an oxaliplatin-containing regimen.[1] 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 panels on colon and rectal cancers prefer Avastin over Zaltrap and Cyramza® (ramucirumab injection for intravenous use) 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

1. **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.

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive.

Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

Prior approval is required for HCPCS Code J9400.

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 2015.
3. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 2.2016). © 2016 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 10, 2016
4. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 3.2015 2.2016). © 2016 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 10, 2016
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. © 2016 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 10, 2016. 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.

HCPCS Code(s):	
J9400	Injection, Ziv-aflibercept, 1 mg