# Medical Policy

**Healthcare Services Department**

| Policy Name | Policy Number | Scope |
|---|---|---|
| **Ziv-aflibercept (Zaltrap®)** | MP-RX-FP-107-23 | ☒ MMM MA ☒ MMM Multihealth |

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B DRUG

## Service Description

This document addresses the use of *Ziv-aflibercept (Zaltrap®),* a vascular endothelial growth factor inhibitor, approved by the Food and Drug Administration (FDA), in combination with fluorouracil, leucovorin, irinotecan (FOLFIRI), for the treatment of metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen.

**Background Information**

Ziv-aflibercept, marketed under the name Zaltrap®, is a recombinant fusion protein. It was previously known as aflibercept and VEGF Trap. This innovative protein functions as a soluble receptor that binds to several critical factors, including vascular endothelial growth factor-A (VEGF-A), VEGF-B, and placental growth factor (PIGF). By binding to these natural ligands, Zaltrap (ziv-aflibercept) has the capacity to inhibit their binding and activation of their respective receptors. This inhibition process leads to a reduction in neovascularization (the formation of new blood vessels) and a decrease in vascular permeability.

Vascular endothelial growth factor (VEGF) is a significant signaling protein that plays a pivotal role in angiogenesis, which is the growth of new blood vessels from existing ones. Ziv-aflibercept is specifically designed to function as a "VEGF trap," preventing the activation of VEGF receptors and thereby hindering the process of angiogenesis. The inhibition of these factors contributes to a decrease in neovascularization and vascular permeability.

On August 3, 2012, the Food and Drug Administration (FDA) granted approval for the use of Zaltrap, in combination with a FOLFIRI (folinic acid, fluorouracil, and irinotecan) chemotherapy regimen to treat metastatic colorectal cancer (MCRC) in adults. The safety and efficacy of Zaltrap were assessed through a randomized clinical study conducted by Van Cutsem et al. in 2012, which involved 1,226 MCRC patients. These patients either experienced cancer growth while on oxaliplatin-based combination chemotherapy or had their cancer surgically removed but had a recurrence within 6 months after receiving oxaliplatin-based combination chemotherapy as adjuvant treatment. Participants in the study received treatment until their cancer progressed or until they found the side effects intolerable. The primary outcome under investigation was overall survival (OS). Among patients who were administered the Zaltrap plus FOLFIRI combination (n = 612), the average survival was 13.5 months, in contrast to the average of 12 months for those who received FOLFIRI plus a placebo (n = 614). Moreover, there was a notable reduction in tumor size observed in 20% of patients receiving the Zaltrap plus FOLFIRI combination, compared to 11% for those on FOLFIRI plus a placebo. Additionally, the clinical trial demonstrated an enhancement in progression-free survival (PFS). Patients receiving the Zaltrap plus FOLFIRI combination experienced a PFS of 6.9 months, while those on FOLFIRI plus a placebo had a PFS of 4.7 months.

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The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for treatment of CRC. NCCN notes that no data exists that suggest activity of FOLFIRI plus Zaltrap in individuals who have progressed on FOLFIRI plus bevacizumab; FOLFIRI + Zaltrap has only shown activity when given to FOLFIRI-naïve individuals.

Within the guidelines, NCCN recommends that appendiceal adenocarcinoma be treated with chemotherapy according to colon cancer guidelines. Similarly, anal adenocarcinoma may be treated according to guidelines for rectal cancer.

In addition, NCCN notes that studies have shown that combination with more than one biologic agent is not associated with improved outcomes and can cause increased toxicity, specifically regarding the addition of Erbitux (cetuximab) or Vectibix (panitumumab) to a bevacizumab-containing regimen (Tol 2009, Hecht 2009). NCCN strongly recommends against the use of therapy involving concurrent combination of an anti-EGFR agent and an anti-VEGF agent.

Individuals using Zaltrap should be monitored for hemorrhage, gastrointestinal perforation, and compromised wound healing. It should be suspended for at least 4 weeks prior to elective surgery and not resumed for at least 4 weeks following major surgery and until surgical wound is fully healed.

Definitions and Measures

- Adenocarcinoma: Cancer originating in cells that line specific internal organs and that have gland-like (secretory) properties.
- Anal cancer: Cancer originating in the tissues of the anus; the anus is the opening of the rectum (last part of the large intestine) to the outside of the body.
- Colon cancer: Cancer originating in the tissues of the colon (the longest part of the large intestine). Most colon cancers are adenocarcinomas that begin in cells that make and release mucus and other fluids.
- Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).
- Disease Progression: Cancer that continues to grow or spread.
- Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.
- One line of therapy: Single line of therapy.
- Progressive Disease (PD): Cancer that is growing, spreading, or getting worse.
- Rectal cancer: Cancer originating in tissues of the rectum (the last several inches of the large intestine closest to the anus). Refractory Disease: Illness or disease that does not respond to treatment.
- Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.
- Unresectable: Unable to be removed with surgery.

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- Vascular endothelial growth factor (VEGF): A substance made by cells that stimulates new blood vessel formation.

**Approved Indications**

The FDA approved indication of Zaltrap is to be used in combination with fluorouracil, leucovorin, irinotecan (FOLFIRI), for the treatment of metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen.

**Other Uses**

NCCN also provides 2A recommendations for Zaltrap in combination with an irinotecan-based regimen for treatment of mCRC that has previously been treated with fluoro-pyrimidine without irinotecan ***or*** oxaliplatin. However, studies cited in this recommendation only investigated Zaltrap after previous treatment with an oxaliplatin-based regimen (Van Cutsem 2012).

## Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

| HCPCS | Description |
|---|---|
| J9400 | Injection, ziv-aflibercept, 1 mg [Zaltrap] |

| ICD-10 | Description |
|---|---|
| C18.0-C18.9 | Malignant neoplasm of colon |
| C19 | Malignant neoplasm of rectosigmoid junction |
| C20 | Malignant neoplasm of rectum |
| C21.0-C21.8 | Malignant neoplasm of anus and anal canal |
| Z85.038 | Personal history of other malignant neoplasm of large intestine |
| Z85.048 | Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus |

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## Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

## Ziv-aflibercept (Zaltrap®)

**A. Criteria For Initial Approval** (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Individual has a diagnosis of advanced or metastatic colon, rectal, colorectal, appendiceal, or anal adenocarcinoma (Label, NCCN 2A); **AND**
ii. The individual is unresectable, resistant to or has disease progression following treatment with an oxaliplatin-containing regimen; **AND**
iii. Ziv-aflibercept will be used in combination with an irinotecan based regimen; **AND**
iv. Ziv-aflibercept will be given in a single line of therapy.

**B. Criteria For Continuation of Therapy**

i. MMM considers continuation of Ziv-aflibercept (Zaltrap®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen. The following information should be submitted for reauthorization:
   A. A current oncology note documenting the patient's response to treatment showing no progression of disease
   B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results

**C. Authorization Duration**

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

**D. Conditions Not Covered**

*Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):*

i. Ziv-aflibercept is given in combination with cetuximab, panitumumab, or bevacizumab (or bevacizumab biosimilar);

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**OR**

ii. Ziv-aflibercept is used in combination with the same irinotecan-based regimen that was previously used in combination with bevacizumab (or bevacizumab biosimilar);

**OR**

iii. When the above criteria are not met and for all other indications.

## Limits or Restrictions

A. Therapeutic Alternatives

*The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.*

i. N/A

B. Quantity Limitations

*Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.*

| Drug | Recommended Dosing Schedule |
|---|---|
| Ziv-aflibercept (Zaltrap®) | 4 mg per kg of actual body weight every two weeks in combination with FOLFIRI until disease progression or unacceptable toxicity. |
| **Exceptions** | |
| None | |

## Reference Information

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: January 16, 2024.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2024; Updated periodically.
4. 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(28):3499-3506.
5. 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(2):320-331.

6. NCCN Clinical Practice Guidelines in Oncology™. © 2024 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on January 16, 2024. a. Colon Cancer. V4.2023. Revised November 16, 2023. b. Rectal Cancer. V6.2023. Revised November 16, 2023. c. Anal Carcinoma. V1.2024. Revised December 20, 2023.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.



## Policy History

| Revision Type | Summary of Changes | P&T Approval Date | MPCC Approval Date |
|---|---|---|---|
| Annual Review 10/24/2025 | Add unresectable disease. Coding Reviewed: Removed ICD-10-CM Z85.068 and C78.5. | 10/31/2025 | 11/10/2025 |
| Annual Review 11/12/2024 | Include advanced disease to initial requests criteria per NCCN. Add Conditions not Covered. Update references and minor wording and formatting updates. Coding Reviewed: No changes. | 3/14/2025 | 4/2/2025 |
| Select Review 2/15/2024 | Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria. | 3/25/2024 | 5/9/2024 |
| Policy Inception 11/12/23 | Elevance Health's Medical Policy adoption. | N/A | 11/30/2023 |