



**Medication Policy Manual**

**Policy No:** dru279

**Topic:** Zaltrap®, ziv-aflibercept

**Date of Origin:** September 24, 2012

**Committee Approval Date:** August 12, 2016

**Next Review Date:** August 2017

**Effective Date:** September 1, 2016

### **IMPORTANT REMINDER**

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

### **Description**

Ziv-aflibercept (Zaltrap) is an intravenously infused Vascular Endothelial Growth Factor (VEGF) inhibitor used in the treatment of metastatic colorectal cancer.

## Policy/Criteria

- I. Most contracts require prior authorization approval of ziv-aflibercept (Zaltrap) prior to coverage. Ziv-aflibercept (Zaltrap) may be considered medically necessary when criteria A, B, and C below are met:
  - A. A diagnosis of metastatic colorectal cancer.

AND

  - B. Prior treatment with an oxaliplatin (Eloxatin)-containing regimen has been ineffective or not tolerated.

AND

  - C. Prior treatment with bevacizumab (Avastin) has been ineffective, contraindicated, or not tolerated.
  
- II. Administration, Quantity Limitations, and Authorization Period
  - A. OmedaRx does not consider ziv-aflibercept (Zaltrap) to be a self-administered medication.
  - B. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
  
- III. Ziv-aflibercept is considered investigational when used for all other conditions, including but not limited to:
  - A. Gastroesophageal cancers
  - B. Kidney cancer
  - C. Leukemia
  - D. Lung cancer (small cell, and non-small cell lung cancers)
  - E. Lymphoma
  - F. Ovarian cancer
  - G. Pancreatic cancer
  - H. Prostate cancer
  - I. Thyroid cancer

## Position Statement

- Ziv-aflibercept (Zaltrap) is an intravenously infused medication that inhibits Vascular Endothelial Growth Factor (VEGF) thereby preventing the formation of new blood vessels and halting cell growth.
- Ziv-aflibercept (Zaltrap) demonstrated an improvement in overall survival in metastatic colorectal cancer that was previously treated with an oxaliplatin-containing regimen.
- Ziv-aflibercept (Zaltrap) was studied in combination with 5-fluorouracil, leucovorin and irinotecan (FOLFIRI).

- Bevacizumab (Avastin) is another VEGF inhibitor approved for the treatment of metastatic colorectal cancer in combination with 5-fluorouracil based chemotherapy.
- There is insufficient evidence to establish the comparative efficacy and safety of bevacizumab and ziv-aflibercept (Zaltrap).
- For OmedaRx members, bevacizumab (Avastin) is the preferred medication among the VEGF inhibitors used to treat metastatic colorectal cancer.
- The safety and effectiveness of ziv-aflibercept (Zaltrap) have not been established in conditions other than metastatic colorectal cancer.

### *Clinical Efficacy*

Ziv-aflibercept (Zaltrap) demonstrated improved overall survival in patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.

- A single, randomized controlled trial compared ziv-aflibercept (Zaltrap) in combination with 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) to FOLFIRI alone in the treatment of patients with metastatic colorectal cancer that was resistant to, or had progressed following, and oxaliplatin-containing regimen. <sup>[1,2]</sup>
  - \* The primary endpoint of the study was overall survival (OS). The addition of ziv-aflibercept (Zaltrap) to FOLFIRI improved OS by 1.44 months compared to FOLFIRI alone (12.06 versus 13.5 months, respectively; p = 0.0032).
  - \* Approximately 30% of randomized patients had received prior treatment with bevacizumab (Avastin).
- The National Comprehensive Cancer Network (NCCN) Colon and Rectal Cancer treatment guidelines list ziv-aflibercept (Zaltrap) as an option (category 2A) after the first progression of metastatic colon or rectal cancer. NCCN recommends that ziv-aflibercept (Zaltrap) be used in combination with FOLFIRI or irinotecan. Bevacizumab (Avastin) also has a category 2A recommendation in this treatment setting. Additionally, bevacizumab (Avastin) has a category 2A recommendation for initial treatment of advanced or metastatic colorectal cancer in combination with FOLFOX or CapeOX. <sup>[3,4]</sup>

**OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN guidelines.**

### *Use in Other Conditions*

Ziv-aflibercept (Zaltrap) is currently being studied for treatment of a variety of cancers, including: leukemia, lung cancer (small cell and non-small cell), lymphoma, ovarian cancer, pancreatic cancer, prostate cancer and thyroid cancer. <sup>[4]</sup> There are currently no published studies supporting the safety or efficacy of ziv-aflibercept (Zaltrap) in these cancers. Preliminary results reported on clinicaltrials.gov show a lack of benefit with ziv-aflibercept (Zaltrap) in non-small cell lung cancer, ovarian cancer, and prostate cancer. <sup>[5]</sup>

### Safety

- Ziv-aflibercept (Zaltrap) has Boxed Warnings for risk of hemorrhage, gastrointestinal perforation, and compromised wound healing. [1]
- Other serious adverse effects reported with ziv-aflibercept (Zaltrap) include fistula formation, hypertension, arterial thromboembolic events, proteinuria, neutropenia, diarrhea and dehydration, and reversible posterior leukoencephalopathy syndrome. [1]
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### Dosing

- The usual dose of ziv-aflibercept is 4 mg/kg given by intravenous infusion over 1 hour every 2 weeks. [1]
- Ziv-aflibercept is indicated for use in combination with 5-fluorouracil, leucovorin and irinotecan (FOLFIRI). [1]

<b>Cross References</b>
Avastin®, bevacizumab, dru215
Erbitux®, cetuximab, dru187

<b>Codes</b>	<b>Number</b>	<b>Description</b>
HCPCS	J9400	Injection, Ziv-Aflibercept, 1 Mg

### References

1. Zaltrap® [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC; October 2013.
2. 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;30:3499-506. PMID: 22949147
3. NCCN Clinical Practice Guidelines in Oncology™. Colon Cancer v.3.2015. [cited 7/13/2015]; Available from: [http://www.nccn.org/professionals/physician\\_gls/pdf/colon.pdf](http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf).
4. NCCN Clinical Practice Guidelines in Oncology™. Rectal Cancer v.3.2015. [cited 7/13/2015]; Available from: [http://www.nccn.org/professionals/physician\\_gls/pdf/rectal.pdf](http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf)
5. Clinicaltrials.gov. [cited 7/25/2014]; Available from: <http://www.clinicaltrials.gov>

<b>Revision Date</b>	<b>Revision Summary</b>
8/12/2016	No criteria changes with this annual update.