



Complete Patient and Physician information (PLEASE PRINT)

STEP 1	Member Name:	Physician Name:
	Address:	Address:
	Member ID:	Phone #:
	Member DOB:	Fax #:
	Member Phone:	NPI Number:

Zaltrap is exclusively provided by Modern Health Specialty Pharmacy Phone: 800-228-3643

Complete the Clinical Assessment:

STEP 2	Diagnosis	<input type="checkbox"/> Metastatic colorectal cancer (mCRC) (documentation required). <input type="checkbox"/> Other (please state): _____
	Clinical Consideration <i>(All criteria must be met for approval)</i>	<input type="checkbox"/> mCRC is resistant to or has progressed following an oxaliplatin-containing regimen. <i>List oxaliplatin-containing regimen and dates of therapy:</i> _____ <input type="checkbox"/> Zaltrap is being used in combination with FOLFIRI (5-fluorouracil, leucovorin, and irinotecan). <input type="checkbox"/> Patient is FOLFIRI naïve.
	Cost and Clinical Acknowledgement	<input type="checkbox"/> I understand that the <i>cost per treatment</i> with <u>Zaltrap</u> is approximately two times more expensive than the cost for <u>Avastin</u> (bevacizumab) AND that both, in combination with FOLFIRI, increase median overall survival ~1.4 months more than FOLFIRI alone.
	Physician Specialty	<input type="checkbox"/> Oncologist <input type="checkbox"/> Other (please state): _____
	Supporting Documentation <i>Please attach all relevant medical records and test results.</i>	Diagnosis: ICD-9/10 Code #/ Description / J Code (required): Please attach a copy of the prescription or provide ALL of the information below: Zaltrap® (ziv-aflibercept) Strength _____ Sig _____ Qty _____ <p style="text-align: center;">We will not process incomplete forms. If we do not receive the completed form and all relevant medical records and test results within 6 calendar days of this request, it will be denied.</p>

STEP 3 **I certify that the above is correct and accurate to the best of my knowledge and that the form is complete. (Please sign and date)**

Prescriber Signature

Date

STEP 4 **Fax completed form, all records & test results to RMHP Pharmacy Help Desk ONLY: 970-248-5034**

Name of Person filling out form: _____

Pharmacy Technician initials _____ Date Initiated _____

Confidentiality Notice:

This facsimile transmission (and/or documents accompanying it) may contain confidential information. This information is intended only for the use of the individual(s) named above. If you have received this transmission in error, or cannot identify the recipient for distribution purposes, please notify us immediately at 970-244-7760. Plans underwritten by Rocky Mountain HMO or Rocky Mountain HealthCare Options. 01/23/14

RMHP Formulary Coverage Policy

THIS INFORMATION IS NOT ALL-INCLUSIVE AND IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY

Zaltrap® (ziv-aflibercept)

CLASSIFICATION

- Antineoplastic Agent
- Recombinant fusion protein
- Vascular Endothelial Growth Factor Inhibitor
- Angiogenesis Inhibitor

DESCRIPTION

- Ziv-aflibercept is a recombinant fusion protein that acts as a soluble receptor that binds to human VEGF-A, VEGF-B, and to placental growth factor (PlGF) and inhibits the binding and activation of their cognate receptors that produce neovascularization and vascular permeability. The result of this binding is decreased neovascularization and decreased vascular permeability.
- Aflibercept is indicated for the treatment of metastatic colorectal cancer (mCRC) in combination with irinotecan plus 5-fluorouracil and leucovorin (FOLFIRI) in adult patients whose disease is resistant to or has progressed following an oxaliplatin-based regimen.
- In a randomized, double-blind, placebo-controlled study (n=1226), overall survival and progression-free survival were significantly improved with the addition of aflibercept to irinotecan plus 5-fluorouracil and leucovorin (FOLFIRI) in adults with mCRC resistant to or that progressed during or within 6 months of receiving oxaliplatin-based chemotherapy, with or without prior bevacizumab.
- **Median overall survival** was significantly longer in patients treated with ziv-aflibercept (13.5 versus 12.1 months for PBO), a **difference of 1.4 months**; p=0.0032
- **Median PFS** was significantly longer in patients treated with ziv-aflibercept (6.9 versus 4.7 months for PBO), a **difference of 2.2 months**; p<0.0001.
- Response rate was 19.8% (95% CI, 16.4% to 23.2%) with ziv-aflibercept/FOLFIRI compared with 11.1% (95% CI, 8.5% to 13.8%) with placebo/FOLFIRI; p = 0.0001.
- There are no data to suggest activity of Zaltrap/FOLFIRI in a patient who has progressed on Avastin/FOLFIRI, or vice versa. Zaltrap has only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients.
- Most common adverse reactions that had $\geq 20\%$ incidence and at least 2% greater incidence for the Zaltrap/FOLFIRI regimen were leucopenia, diarrhea, neutropenia, proteinuria, AST increased, Stomatitis, fatigue, thrombocytopenia, ALT increased, hypertension, weight decreased, decreased appetite, epistaxis, abdominal pain, dysphonia, serum creatinine increased, and headache.

FORMULARY COVERAGE

Prior authorization: Required

Good Health Formulary: Tier 6

Commercial Formulary: Tier 6

Medicare Part D coverage: Tier 5

COVERAGE CRITERIA

Zaltrap® (ziv-aflibercept) meets the definition of **medical necessity** for the following:

- Aflibercept is indicated for the treatment of metastatic colorectal cancer (mCRC) in combination with irinotecan plus 5-fluorouracil and leucovorin (FOLFIRI) in adult patients whose disease is resistant to or has progressed following an oxaliplatin-based regimen.
- Documentation of diagnosis and resistant or refractory oxaliplatin-based regimen is required for approval.

- *NOTE: For use of aflibercept for exudative age-related macular degeneration, see prior authorization form for Eylea (aflibercept).*

Zaltrap® (ziv-aflibercept) is considered **experimental** for the following:

- Any condition or diagnosis not FDA approved or Compendia supported.
- *NOTE:* Currently there is no data to suggest activity of Zaltrap/FOLFIRI in a patient who has progressed on Avastin/FOLFIRI, or vice versa. Zaltrap has only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients. Until high-level evidence is available demonstrating benefit with Zaltrap/FOLFIRI after failure or progression on Avastin/FOLFIRI, this sequence of treatment will not be covered.

Required Provider Specialty:

- Approval is limited to Oncology

DOSAGE/ADMINISTRATION

Adult Dosing (safety and efficacy has not been determined for pediatric patients):

- mCRC in combination with FOLFIRI:
 - Recommended dose is 4 mg/kg IV infused over 1 hour every 2 weeks.
 - Administer aflibercept prior to any component of FOLFIRI regimen on day of treatment.
 - Continue treatment for as long as a clinical benefit is seen or until unacceptable toxicity occurs

Geriatric Dosing:

- No dosage adjustment is required in patients 65 years of age or older

Dosing in other disease states:

- **Elective Surgery:** Withhold aflibercept therapy for at least 4 weeks prior to elective surgery. Do not resume therapy for at least 4 weeks following a major surgical procedure and until the surgical wound is completely healed. Following minor surgical procedures (e.g. central venous access port placement, biopsy, tooth extraction), resume/start aflibercept once the surgical wound is fully healed.
- **Hypertension:** If recurrent or severe hypertension occurs during the course of aflibercept therapy, interrupt therapy and withhold dose until blood pressure is controlled. Reinitiate aflibercept at a permanently reduced dose of 2 mg/kg IV for subsequent cycles. If hypertensive crisis or hypertensive encephalopathy occur, permanently discontinue aflibercept
- **Proteinuria:** If proteinuria of 2 g/24 hours or more occurs during the course of aflibercept therapy, interrupt therapy and withhold dose until proteinuria recovers to less than 2 g/24 hours, and resume. If proteinuria of 2 g/24 hours or more recurs, interrupt therapy and withhold dose until proteinuria recovers to less than 2 g/24 hours and reinitiate aflibercept at a permanently reduced dose of 2 mg/kg IV for subsequent cycles. If nephrotic syndrome or thrombotic microangiopathy occurs, permanently discontinue aflibercept.

PRECAUTION

Black Box Warning:

- **Hemorrhage:** Severe and sometimes fatal hemorrhage, including gastrointestinal (GI), intracranial, and pulmonary hemorrhage, have been reported in the patients who have received aflibercept in combination with FOLFIRI. Monitor patients for signs and symptoms of GI bleeding and other severe bleeding. Do not administer aflibercept to patients with severe hemorrhage. Bleeding/hemorrhage (all grades) were reported in 38% of patients treated with Zaltrap/FOLFIRI compared to 19% of patients treated with placebo/FOLFIRI.
- **Gastrointestinal Perforation:** GI perforation including fatal GI perforation can occur in patients receiving aflibercept. Discontinue aflibercept therapy in patients who experience GI perforation.
- **Compromised Wound Healing:** Severe compromised wound healing can occur in patients receiving aflibercept/FOLFIRI. Discontinue aflibercept in patients with compromised wound healing.

Precautions:

- Elective surgery: suspend therapy for at least 4 weeks prior to, and do not resume for at least 4 weeks following major surgery and until the surgical wound is fully healed after major or minor surgery.
- Arterial thromboembolic events (e.g. angina, transient ischemic attack, cerebrovascular accident) have been reported; discontinuation required.
- The incidence of severe diarrhea is increased in patients treated with Zaltrap/FOLFIRI. In patients with mCRC, Grade 3–4 diarrhea was reported in 19% of patients treated with ZALTRAP/FOLFIRI compared to 8% of patients treated with placebo/FOLFIRI.
- Grade 3–4 dehydration was reported in 4% of patients treated with Zaltrap/FOLFIRI compared to 1% of patients treated with placebo/FOLFIRI.
- Geriatric patients have higher incidences of adverse events (e.g. diarrhea, dizziness, asthenia, weight decrease, dehydration). Monitoring for diarrhea and dehydration is recommended.
- Fistulas of gastrointestinal and non-gastrointestinal sites have been reported; discontinuation required.
- Hypertension, grade 3/4 including hypertensive crisis, has been reported. Monitoring is required and dosage adjustment, suspension and/or discontinuation of therapy may be needed.
- Nephrotic syndrome and thrombotic microangiopathy (TMA) have been reported. Monitoring is required, as is discontinuation of Zaltrap if it occurs.
- Neutropenic complications, grade 3/4, including febrile neutropenia and neutropenic infection have been reported and require monitoring. Interruption of therapy may be needed.
- Reversible posterior leukoencephalopathy syndrome (RPLS) has been reported in 0.5% of 3795 patients treated with Zaltrap monotherapy or in combination with chemotherapy. Confirm the diagnosis of RPLS with MRI and discontinue Zaltrap in patients who develop RPLS. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae or death.
- Severe proteinuria has been reported and requires monitoring. Adjustment of dose or suspension may be needed. Proteinuria was reported in 62% patients treated with Zaltrap/FOLFIRI compared to 41% patients treated with placebo/FOLFIRI.

Billing/Coding information

HCPCS Coding:

C 9296	Injection, ziv-aflibercept, 1mg
J 9999	Not otherwise classified, antineoplastic drugs

COST

- AWP (September 2012): Zaltrap (ziv-aflibercept) 100mg/4ml vial (1 vial): \$1,920.00
Zaltrap (ziv-aflibercept) 200mg/8ml vial (1 vial): \$3,840.00

COMMITTEE APPROVAL

- September 2012

GUIDELINE UPDATE INFORMATION

September 2012	Prior Authorization and Coverage Policy created

REFERENCES

- DRUGDEX®, accessed 09/15/2012.
- Product Information: Zaltrap® (ziv-aflibercept), injection for Intravenous Infusion. Regeneron Pharmaceuticals, Inc. / sanofi-aventis U.S. LLC, Bridgewater, NJ, 2012.
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Colon Cancer. ©National Comprehensive Cancer Network, Inc. Version 1.2013, 8/29/12. Accessed 9/15/2012.
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Colon Cancer. ©National Comprehensive Cancer Network, Inc. Version 2.2013, 09/10/12. Accessed 9/15/2012.
- Clark JW, Grothey A. Systemic Chemotherapy for Nonoperable Metastatic Colorectal Cancer: Treatment. UpToDate® Topic 2470 Version 37.0. Accessed 09/15/2012.