I. PURPOSE
To define and describe the accepted indications for Zaltrap (ziv-aflibercept) usage in the treatment of cancer

II. DEFINITIONS
Zaltrap (ziv-aflibercept): is an angiogenesis inhibitor. It is a fully humanized recombinant fusion protein that acts as a soluble receptor to bind vascular endothelial growth factor (VEGF)-A, VEGF-B, and placental growth factors 1 and 2, which prevents other native receptors from binding. Inhibition of native receptor binding can result in decreased neovascularization and decreased vascular permeability. In animals, ziv-aflibercept inhibited the growth of new blood vessels through inhibition of endothelial cell proliferation. Also, in mice, ziv-aflibercept inhibited the growth of xenotransplanted colon tumors.

Zaltrap (ziv-aflibercept), in combination with FOLFIRI, is FDA approved for the treatment of patients with metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing chemotherapy regimen.

Zaltrap (ziv-aflibercept) is available as an injection solution: 100mg and 200 mg single-use vials.

III. POLICY
New Century is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century may be deemed as not approvable and therefore not reimbursable.

Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must follow CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.

Inclusion Criteria: Zaltrap (ziv-aflibercept) may be considered medically necessary when any of the following selection criteria is met:

1. Colorectal Cancer
   a. Zaltrap (ziv-aflibercept) is being used in members with the following:
      i. Stage IV unresectable metastatic colorectal cancer AND
      ii. In combination with irinotecan or with FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen AND
iii. After first progression of advanced or metastatic disease in members not previously receiving irinotecan-based regimens (i.e. FOLFIRI) OR

iv. After first progression, within the past 12 months, of adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) regimen.

**Exclusion Criteria:** Zaltrap (ziv-aflibercept) is not considered medically necessary when any of the following selection criteria is met:

1. Zaltrap (ziv-aflibercept) is not being used in members with any of the following:
   a. Non-metastatic disease
   b. As first line therapy without resistance to or has progressed following an oxaliplatin-based regimen or irinotecan-based regimen.
   c. Within 4 weeks prior to and 4 weeks following surgery and not until surgical wound is fully healed.
   d. Progression of disease while on Zaltrap (ziv-aflibercept) or restarted after progression of disease.
2. Dosing exceeds single dose limit of Zaltrap (ziv-aflibercept) 4mg/kg every 2 weeks.
3. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

**IV. PROCEDURE**

Requests for Zaltrap (ziv-aflibercept) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. **Dosage and Administration:** 4 mg/kg IV infused over 1 hour every 2 weeks. Administer aflibercept prior to irinotecan based regimen on day of treatment. Continue treatment for as long as a clinical benefit is seen or until unacceptable toxicity occurs.

2. **Dosage Adjustments:** Dosage adjustments are not required for renal or hepatic impairment.
   a. Elective surgery: interrupt therapy for at least 4 weeks prior to procedure; do not resume therapy for at least 4 weeks following a major surgical procedure and until the surgical wound is completely healed.
   b. Hypertension, severe or recurrent: temporarily interrupt therapy until controlled, reinitiate and permanently reduce dose to 2 mg/kg IV; discontinue use if hypertensive crisis or hypertensive encephalopathy occur.
   c. Proteinuria, 2 g/24 hours: interrupt therapy until proteinuria recovers to less than 2 g/24 hours and resume; if proteinuria recurs, interrupt therapy again until proteinuria recovers to less than 2 g/24 hours and reinitiate at permanently reduced dose of 2 mg/kg IV; discontinue use if nephrotic syndrome or thrombotic microangiopathy occur.

3. **Monitoring**
   a. Evidence of disease response or stabilization indicates efficacy.
   b. Monitor CBC with differential at baseline and prior to initiation of each cycle of aflibercept.
   c. Monitor blood pressure every 2 weeks during therapy or more frequently as clinically indicated.
d. Monitor urine protein by urine dipstick analysis and urinary protein creatinine ratio (UPCR) for
development or worsening of proteinuria during therapy and obtain a 24-hour urine collection
in patients with UPCR greater than one.

V. APPROVAL AUTHORITY

1. Review – UM Department
2. Final Approval – UM Committee

VI. ATTACHMENTS

None

VII. REFERENCES

   2018.
5. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs.
   Bethesda, MD. 2018.