Effective November 1, 2018, refer to Palmetto Article A56141

BlueCross BlueShield of Alabama

"Unless otherwise noted, coverage for specific indications is effective the date of the FDA approval of that indication."
"Please check Approved by Governing Bodies for FDA approval date."

Name of Blue Advantage Policy:

Zaltrap® (ziv-aflibercept)

Policy #:	665	Effective Date:	September 1, 2015
Category:	Pharmacy	Last Review Date:	May 2018

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Zaltrap® (zil-aflibercept) is a recombinant fusion protein consisting of vascular endothelial growth factor (VEGF)-binding portions from the extracellular domains of human VEGF receptors 1 and 2 that are fused to the Fc portion of the human IgG1 immunoglobulin. VEGF is responsible for creating new blood vessels to assure adequate perfusion of blood or oxygen. Inhibition of VEGF is one of the methods used in cancer treatment by cutting blood supply to cancer cells. It acts as a soluble receptor that binds to vascular endothelial growth factor-A (VEGF-A), VEGF-B, and placental growth factor (PIGF). Inhibition of these factors can result in decreased neovascularization and decreased vascular permeability. The drug is an angiogenesis inhibitor that inhibits blood supply to tumors. It is intended for patients whose cancer has spread to other parts of the body (metastatic) and whose tumors are resistant to or progressed after an oxaliplatin-containing chemotherapy regimen.

Policy:

Effective for dates of service on or after November 1, 2018 refer to Palmetto Article A56141

Effective for dates of service prior to November 1, 2018:

Blue Advantage will treat **Zaltrap® (ziv-aflibercept)** as a **covered benefit** when **ALL** of the following criteria are met:

- The individual has advanced or metastatic colorectal cancer, small intestine adenocarcinoma, appendiceal adenocarcinoma, or anal adenocarcinoma which is resistant to or has progressed following treatment with an oxaliplatin-containing regimen**; AND**
- Zaltrap will not be used in combination with other targeted therapy, including cetuximab, panitumumab, or bevacizumab; **AND**
- Zaltrap (ziv-aflibercept) will be used in combination with an irinotecan based regimen; **AND**
- Zaltrap (ziv-aflibercept) will be given in a single line of therapy

Blue Advantage will treat **Zaltrap® (ziv-aflibercept)** as a **non-covered benefit** and as **investigational** when used in combination with the same irinotecan based regimen that was previously used in combination with bevacizumab.

Blue Advantage will treat **Zaltrap® (ziv-aflibercept)** as a **non-covered benefit** and as **investigational** when the above criteria are not meet.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most

appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. According to the National Institutes for Health, in 2017 estimated 140, 250 Americans will be diagnosed with colon and rectal cancer and an estimated 50, 630 will die from colon and rectal cancer combined.

The ZALTRAP approval was based on data from the pivotal Phase III VELOUR trial, a multinational, randomized, double-blind trial comparing FOLFIRI in combination with either ZALTRAP or placebo in the treatment of patients with mCRC. The study randomized 1,226 patients with mCRC who previously had been treated with an oxaliplatin -containing regimen. Twenty-eight percent of patients in the study received prior bevacizumab therapy. Treatment continued until disease progression or unacceptable toxicity. The primary endpoint was overall survival. Secondary endpoints included progression-free survival, overall response rate, and safety.

The VELOUR trial showed that in patients previously treated with an oxaliplatin containing regimen, adding ZALTRAP to FOLFIRI significantly improved median survival from 12.06 months to 13.50 months (HR=0.817 (95% CI 0.714 to 0.935; p=0.0032), an 18 percent relative risk reduction. A significant improvement in progression-free survival from 4.67 months to 6.90 months (HR=0.758 95% CI 0.661 to 0.869; p=0.00007), a 24% relative risk reduction, was also observed. The overall response rate in the ZALTRAP plus FOLFIRI arm was 19.8% vs. 11.1% for FOLFIRI (p=0.0001).

In a phase II trial, Tang and colleagues (2012) investigated the safety and efficacy of aflibercept in adults with metastatic colorectal cancer (mCRC) who had received at least one prior palliative regimen. A total of 75 subjects were enrolled in 2 cohorts, bevacizumab naïve (n=24) and prior bevacizumab (n=51). Aflibercept was administered at 4 mg/kg IV in 2-week cycles. The primary endpoint was a combination of objective response rate and 16-week PFS. In the bevacizumab-naïve cohort, the best response was stable disease for 16 weeks or more in 5 of 24 subjects. In the prior bevacizumab cohort, 1 subject achieved a partial response and 6 had stable disease for 16 weeks or more. The median PFS in the bevacizumab-naïve and prior bevacizumab cohorts was 2 months and 2.4 months, respectively. Median OS was 10.4 months and 8.5 months, respectively. The most common grade 3 or higher treatment-related adverse events were hypertension, proteinuria, fatigue, and headache. Ten subjects discontinued study treatment due to toxicity. Mean free to VEGF-bound aflibercept ratio was 1.82, suggesting that free aflibercept was present in sufficient amount to bind endogenous VEGF. The authors concluded that aflibercept showed limited single-agent activity in those with pretreated mCRC with moderate toxicity.

In a post hoc extended analysis of the VELOUR trial, Joulain and colleagues (2013) estimated the difference in mean survival between the trial's treatment groups with statistical analysis by extrapolating study survival curves. Mean OS was calculated over a 15-year survival period and

the estimated difference between aflibercept+FOLFIRI and placebo+FOLFIRI was 4.7 months. The survival advantage with aflibercept was found to be at least 3 months for the intention to treat population.

Tabernero and colleagues (2014) performed a pre-specified subgroup analysis from the VELOUR trial. Of specific interest were the outcomes of individuals stratified by prior treatment with or without bevacizumab. Median OS, for aflibercept versus placebo was found to be 12.5 (10.8-15.5) versus 11.7 (9.8-13.8) in individuals with prior bevacizumab treatment and 13.9 (12.7-15.6) versus 12.4 (11.2-13.5) in those without prior bevacizumab treatment. The authors concluded that the benefits of aflibercept in combination with FOLFIRI in individuals with mCRC previously treated with oxaliplatin were maintained across the specified subgroups, including in cases with or without prior bevacizumab treatment.

In 2015, Ruff and colleagues reported on the safety and OS benefit of aflibercept over the time course of the VELOUR trial. A total of 1226 subjects had been randomized to treatment consisting either of FOLFIRI and placebo (n=614) or FOLFIRI and aflibercept (n=612). There were 863 deaths (460 in the placebo arm and 403 in the aflibercept arm) on which this analysis was based. The estimated survival probabilities were 38.5% vs 30.9% at 18 months, 28% vs 18.7% at 24 months and 22.3% vs 12.0% at 30 months for the aflibercept and placebo-treated groups, respectively. Common adverse events were diarrhea, stomatitis, infection and hypertension. Most of the grade 3-4 adverse events associated with aflibercept occurred during the early treatment cycles and decreased with later cycles. The majority of adverse events were of single occurrence. Fatal adverse events with aflibercept and FOLFIRI (2.3%) were less in number or comparable to those reported for other regimens used for second line therapy of mCRC. The authors concluded:

> the present survival analysis of the VELOUR trial over different time points up to 30 months demonstrates an increase in survival probability over time for those treated with FOLFIRI plus aflibercept and a persistence of the survival benefit beyond the median survival time of 13.5 months.

The National Comprehensive Cancer Network (NCCN) Colon Clinical Practice Guidelines in Oncology™ (V2. 2018) state that ziv-aflibercept "has only shown activity when given in conjunction with FOLFIRI in FOLFIRI naïve patients." Additionally, NCCN reports a lack of data to suggest activity of FOLFIRI with ziv-aflibercept in individuals who progressed on FOLFIRI plus bevacizumab or vice-versa, and no data to suggest activity of single agent ziv-aflibercept. NCCN recommends adding ziv-aflibercept as a second-line treatment option in combination with FOLFIRI or irinotecan only following progression on therapy not containing irinotecan.

Small bowel, appendiceal, and anal adenocarcinomas

Small bowel and appendiceal adenocarcinomas are rare cancers and the limited data for therapy consists mainly of small retrospective reports and case series. NCCN guidelines for colon cancer (V2.2018) indicate that small bowel and appendiceal adenocarcinoma may be treated with systemic chemotherapy according to their colon cancer guidelines. Anal adenocarcinoma is also very rare, and there is a lack of published literature identifying treatment of this tumor with ziv-

aflibercept. NCCN guidelines for anal carcinoma indicate that anal adenocarcinoma is managed according to their guidelines for rectal cancer. Also of note, NCCN limits ziv-aflibercept treatment to metastatic colorectal cancer and as such, treatment of anal, small bowel, and appendiceal adenocarcinoma should be limited accordingly.
Zaltrap contains a boxed warning advising the agent may cause severe and sometimes fatal hemorrhage, including gastrointestinal (GI) hemorrhage, GI perforation, or severe compromised wound healing.

Key Words:

Metastatic colorectal cancer (mCRC), vascular endothelial growth factor (VEGF), Placental growth factor (PIGF), angiogenesis inhibitor, Zaltrap, ziv-aflibercept

Approved by Governing Bodies:

On August 3, 2012 the U.S. Food and Drug Administration approved ZALTRAP® (Ziv-aflibercept) for use in combination with a FOLFIRI (folinic acid, fluorouracil and irinotecan) chemotherapy regimen to treat adults with metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

HCPCS Codes

J9400 Injection, ziv-aflibercept, 1 mg

References:

1. Czaykowski P, Hui D. Chemotherapy in small bowel adenocarcinoma: 10-year experience of the British Columbia Cancer Agency. Clin Oncol (R Coll Radiol). 2007; 19(2):143-149.
2. Gibson MK, Holcroft CA, Kvols LK, Haller D. Phase II study of 5-fluorouracil, doxorubicin, and mitomycin C for metastatic small bowel adenocarcinoma. Oncologist. 2005; 10(2):132-137.
3. Joulain F, Proskorovsky I, Allegra C, et al. Mean overall survival gain with aflibercept plus FOLFIRI vs placebo plus FOLFIRI in patients with previously treated metastatic colorectal cancer. Br J Cancer. 2013; 109(7):1735-1743.
4. National Cancer Institute (NCI). Colon cancer treatment (PDQ®). Available at: www.cancer.gov/cancertopics/pdq/treatment/colon/HealthProfessional/page11/AllPages.
5. National Cancer Institute. A Snapshot of Colorectal Cancer. Incidence and Mortality. Available at: www.cancer.gov/research/progress/snapshot/colorectal.

6. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Colon and Rectum Cancer. Available at: www.seer.can.gov/statfacts/html/colorect.html.
7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Anal Carcinoma V2.2017. Available at: www.nccn.org.
8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V2.2017. Available at: www.nccn.org.
9. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer V3.2017. Available at: www.nccn.org/index.asp
10. 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(1):18-26.
11. 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.
12. Tang PA, Cohen SJ, Kollmannsberger C, et al. Phase II clinical and pharmacokinetic study of aflibercept in patients with previously treated metastatic colorectal cancer. Clin Cancer Res. 2012; 18(21):6023-6031.
13. 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 oxaliplatin-based regimen. J. Clin Oncol. 2012; 30(28): 3499-3506.
14. Wang TF, Lockhart AC. Aflibercept in the treatment of metastatic colorectal cancer. Clin Med Insights Oncol. 2012; 6:19-30.
15. Zaltrap. [Product Information], Bridgewater, NJ. Sanofi-Aventis U.S. LLC, September 2014. Available at: www.zaltrap.com
16. Ziv-Aflibercept. www.fda.gov/drugs/informationondrugs/approveddrugs/ucm314438.htm
17. Ziv-aflibercept (Rx)-Zaltrap. //reference.medscape.com/drug/zaltrap-ziv-aflibercept-999765.

Policy History:

Medical Policy Group, September 1, 2015.
Medical Policy Group, July 2016
Medical Policy Group, July 2017
Medical Policy Group, May 2018
Medical Policy Group, November 2018