MEDICAL POLICY

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POLICY TITLE	ZIV-AFLIBPERCEPT ZALTRAP
POLICY NUMBER	MP-2.170

Original Issue Date (Created):	**October 30, 2012**
Most Recent Review Date (Revised):	**November 26, 2013**
Effective Date:	**February 01, 2014**

I. POLICY

Note: Zaltrap® (ziv-aflibercept), does not require preauthorization.

U.S. Food and Drug Administration (FDA) indications and usage:

Zaltrap® (ziv-aflibercept), in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

Pediatric Use: The safety and effectiveness of Zaltrap® (ziv-aflibercept) in pediatric patients have not been established.

Zaltrap® (ziv-aflibercept), may be considered **medically necessary** for the treatment of metastatic colorectal cancer (mCRC) when the following conditions are met:

- age ≥18
- mCRC has progressed during or within 6 months of receiving oxaliplatin-based combination chemotherapy
- is given in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI)

Cross-reference:
MP-2.103 Off-Label Use of Prescription Drug and Medical Devices

II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[N] SeniorBlue HMO
[N] SeniorBlue PPO
[N] Indemnity
[N] SpecialCare
[N] POS
[Y] FEP PPO*

* Refer to FEP Medical Policy Manual MP-5.04.25 Zaltrap. The FEP Medical Policy manual can be found at: www.fepblue.org

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III. DESCRIPTION/BACKGROUND

Colorectal cancer is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer death in the United States. According to the National Institutes for Health, an estimated 143,460 Americans will be diagnosed with colorectal cancer and 51,690 will die from the disease in 2012.

On August 3, 2012, the U. S. Food and Drug Administration approved ziv-aflibercept injection (Zaltrap, Sanofi U.S., Inc.) for use in combination with 5-fluorouracil, leucovorin, irinotecan (FOLFIRI) for the treatment of patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen. Ziv-aflibercept (previously known as 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. Inhibition of these factors can result in decreased neovascularization and decreased vascular permeability.

This approval is based on the results of a randomized, double-blind, placebo-controlled, global, multicenter trial enrolling patients with mCRC that progressed during or within 6 months of receiving oxaliplatin-based combination chemotherapy, with or without prior bevacizumab.

The Phase 3 trial accrued 1226 patients who were randomly allocated (1:1) to receive FOLFIRI (irinotecan 180 mg/m^2 IV infusion over 90 minutes, leucovorin 400 mg/m^2 IV infusion over 2 hours, followed by 5-FU 400 mg/m^2 IV bolus, followed by 5-FU 2400 mg/m^2 continuous IV infusion over 46-hours) with either ziv-aflibercept (N=612) or placebo (N=614). Ziv-aflibercept was administered at a dose of 4 mg/kg IV infusion over 1 hour prior to FOLFIRI. The treatment cycles on both arms were repeated every 2 weeks. Patients were treated until disease progression or unacceptable toxicity. The primary efficacy endpoint was overall survival (OS). Treatment assignment was stratified by the ECOG performance status and prior exposure to bevacizumab.

Median age of randomized patients was 61 years, 59% were men, and 98% had an ECOG performance status of 0 or 1. All patients had received prior oxaliplatin treatment. A statistically significant improvement in OS was observed in patients receiving FOLFIRI plus ziv-aflibercept compared to those receiving FOLFIRI plus placebo [HR 0.82 (95% CI: 0.71, 0.94), p=0.0032, stratified log-rank test]. The median OS was 13.5 and 12.06 months for patients on the ziv-aflibercept and placebo arms, respectively. Median progression-free survival in the ziv-aflibercept arm was 6.9 compared to 4.7 months in the placebo arm [HR 0.76 (95% CI: 0.66, 0.87), p=0.00007].

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The most common adverse reactions, (all grades), occurring in ≥ 20% of patients in the ziv-aflibercept plus FOLFIRI arm (with ≥ 2% difference between arms) were leukopenia, diarrhea, neutropenia, proteinuria, increased AST and ALT, stomatitis, fatigue, thrombocytopenia, hypertension, decreased weight, decreased appetite, epistaxis, abdominal pain, dysphonia, increased serum creatinine, and headache. The most common grade 3-4 adverse reactions (≥ 5%) reported at a higher incidence in the ziv-aflibercept plus FOLFIRI arm (≥ 2% difference between arms) were neutropenia, diarrhea, hypertension, leukopenia, stomatitis, fatigue, proteinuria, and asthenia.

Severe and sometimes fatal hemorrhages, including gastrointestinal hemorrhages, have been reported in patients receiving ziv-aflibercept. Grade 3-4 hemorrhagic events occurred in 2.9% of patients receiving FOLFIRI plus ziv-aflibercept compared with 1.7% of those receiving FOLFIRI plus placebo. In addition to hemorrhage, the ziv-aflibercept label contains a Boxed Warning for the serious adverse reactions gastrointestinal perforation and compromised wound healing.

Arterial thromboembolic events were observed in 1.7% and 2.6% of patients in the placebo and ziv-aflibercept containing arms, respectively. Venous thromboembolic events were also observed more frequently with ziv-aflibercept: 9% patients in the ziv-aflibercept-containing arm compared to 7% in the placebo-containing arm. Fistula formation and reversible posterior leukoencephalopathy syndrome have also been reported in patients who received ziv-aflibercept.

The recommended ziv-aflibercept dose and schedule is 4 mg/kg administered as a 60-minute IV infusion every 2 weeks in combination with the FOLFIRI regimen.

Full prescribing information, including Boxed Warning, clinical trial information, safety, dosing, and use in specific populations are available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125418s000lbl.pdf[1]

In the second-line setting, Zaltrap will compete with other targeted therapies for treating mCRC including Erbitux® (cetuximab – Lilly/BMS), Vectibix® (panitumumab - Amgen) and Avastin® (bevacizumab).

IV. RATIONALE

Study 1 was a randomized, double-blind, placebo-controlled study in patients with metastatic colorectal cancer (mCRC) who are resistant to or have progressed during or within 6 months of receiving oxaliplatin-based combination chemotherapy, with or without prior bevacizumab. A total of 1226 patients were randomized (1:1) to receive either ZALTRAP (N=612; 4 mg per kg

as a 1 hour intravenous infusion on day 1) or placebo (N=614), in combination with 5-fluorouracil plus irinotecan [FOLFIRI: irinotecan 180 mg per m2 IV infusion over 90 minutes and leucovorin (dl racemic) 400 mg per m2 intravenous infusion over 2 hours at the same time on day 1 using a Y-line, followed by 5-FU 400 mg per m2 intravenous bolus, followed by 5-FU 2400 mg per m2 continuous intravenous infusion over 46-hours].

The treatment cycles on both arms were repeated every 2 weeks. Patients were treated until disease progression or unacceptable toxicity. The primary efficacy endpoint was overall survival. Treatment assignment was stratified by the ECOG performance status (0 versus 1 versus 2) and according to prior therapy with bevacizumab (yes or no). Demographics characteristics were similar between treatment arms. Of the 1226 patients randomized, the median age was 61 years, 59% were men, 87% were White, 7% were Asian, 3.5% were Black, and 98% had a baseline ECOG performance status (PS) of 0 or 1. Among the 1226 randomized patients, 89% and 90% of patients treated with placebo/FOLFIRI and ZALTRAP/FOLFIRI, respectively, received prior oxaliplatin-based combination chemotherapy in the metastatic/advanced setting. A total of 346 patients (28%) received bevacizumab in combination with the prior oxaliplatin-based treatment.Overall efficacy results for the ZALTRAP/FOLFIRI regimen versus the placebo/FOLFIRI regimen are summarized in Figure 1 and Table 2.

Figure 1 – Overall survival (months) – Kaplan-Meier curves by treatment group

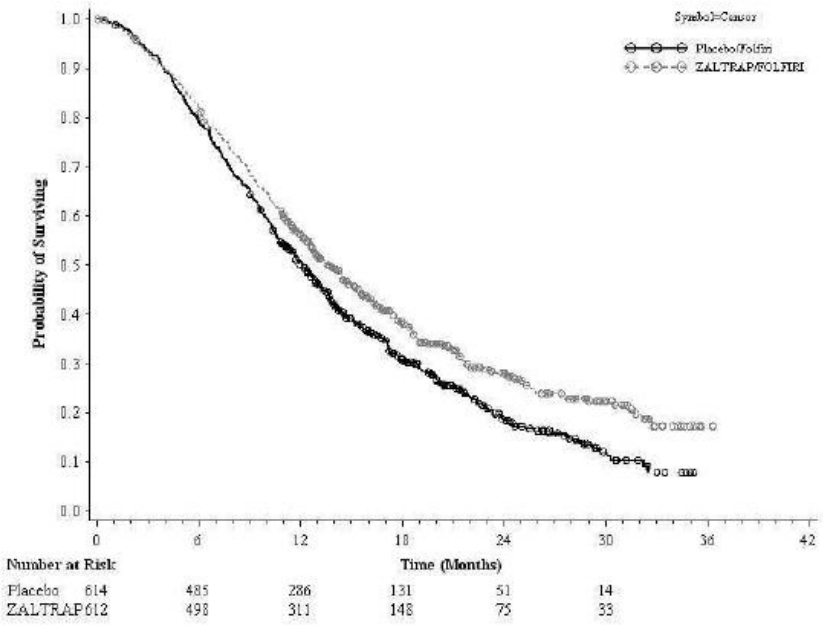

Table 2 Main efficacy outcome measures*

	Placebo/FOLFIRI (N=614)	ZALTRAP/FOLFIRI (N=612)
Overall Survival		
Number of deaths, n (%)	460 (74.9%)	403 (65.8%)
Median overall survival (95% CI) (months)	12.06 (11.07 to 13.08)	13.50 (12.52 to 14.95)
Stratified Hazard ratio (95% CI)	0.817 (0.714 to 0.935)	
Stratified Log-Rank test p-value	0.0032	
Progression Free Survival (PFS)*		
Number of events, n (%)	454 (73.9%)	393 (64.2%)
Median PFS (95% CI) (months)	4.67 (4.21 to 5.36)	6.90 (6.51 to 7.20)
Stratified Hazard ratio (95% CI)	0.758 (0.661 to 0.869)	
Stratified Log-Rank test p-value †	0.00007	
Overall Response Rate (CR+PR) (95% CI) (%)‡	11.1 (8.5 to 13.8)	19.8 (16.4 to 23.2)
Stratified Cochran-Mantel-Haenszel test p-value	0.0001	

*PFS (based on tumor assessment by the IRC): Significance threshold is set to 0.0001.
†Stratified on ECOG Performance Status (0 vs 1 vs 2) and Prior Bevacizumab (yes vs no)
‡Overall objective response rate by IRC

Planned subgroup analyses for overall survival based on stratification factors at randomization yielded an HR of 0.86 (95% CI: 0.68 to 1.1) in patients who received prior bevacizumab and an HR of 0.79 (95% CI: 0.67 to 0.93) in patients without prior bevacizumab exposure.

V. DEFINITIONS

N/A

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this

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medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. REFERENCES

BCBSA TEC Specialty Pharmacy Report #12-2012. Ziv-Aflibercept (Zaltrap®).

Centers for Medicare and Medicaid Services (CMS) Medicare Benefit Policy Manual. Publication 100-02. Chapter 15. Section 50.4.2. Unlabeled Use of Drug. Effective 10/01/03. [Website]: http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/bp102c15.pdf Accessed October 2, 2013.

FDA U.S. Food and Drug Administration. Ziv-aflibercept. [Website]: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm314438.htm?source=govdelivery. Accessed October 2, 2103.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology.Colon Cancer. Version 1. 2014 [Website]: at:http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed October 2, 2013.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Rectal Cancer. Version 1. 2014. [Website]: http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed September 20 2012.

No author listed. FDA news release. U.S. FDA Approves ZALTRAP® (ziv-aflibercept) After Priority Review for Previously Treated Metastatic Colorectal Cancer. Sanofi [Website]: http://sanofi.mediaroom.com/2012-08-03-U.S.-FDA-Approves-ZALTRAP-ziv-aflibercept-After-Priority-Review-for-Previously-Treated-Metastatic-Colorectal-Cancer Accessed October 2, 2013.

Zaltrap® (ziv-aflibercept) prescribing information. Revised 08/2012. Zaltrap[Website]: http://products.sanofi.us/zaltrap/zaltrap.pdf. *Accessed October 2, 2103.*

IX. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

HCPCS Code	Description
J9400	Injection , Ziv Aflibercept, 1mg

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ICD-9-CM Diagnosis Code*	Description
153.0-153.9	Malignant neoplasm of colon
154.0-154.8	Malignant neoplasm of rectum, rectosigmoid junction and anus
197.5	Secondary malignant neoplasm of Large intestine and rectum
209.10-209.17	Malignant carcinoid tumor of the large intestine
209.26	Malignant carcinoid tumor of the midgut
209.27	Malignant carcinoid tumor of the hindgut

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2014

ICD-10-CM Diagnosis Code*	Description
C18.0 –C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.1	Malignant neoplasm of the anal canal
C21.0	Malignant neoplasm of the anus, unspecified
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

X. POLICY HISTORY

MP-2.170	**CAC 10/30/12** New policy. Medically necessary with criteria. Codes added to policy 9/17/12 klr
	02/28/2013- J code added to policy
	CAC 11/26/13 Consensus review. References updated. No changes to the policy statements. Rationale added. FEP variation added to refer to the FEP medical policy manual. Medicare variation removed.