Clinical Policy Bulletin: Ziv-Aflibercept (Zaltrap)

Number: 0842

Policy

Note: REQUIRES PRECERTIFICATION*

Aetna considers ziv-aflibercept (Zaltrap) medically necessary for the treatment of adults with advanced or metastatic colorectal cancer, small intestine adenocarcinoma, appendiceal adenocarcinoma, or anal adenocarcinoma (see Appendix for selection criteria).

Aetna considers ziv-aflibercept experimental and investigational for the treatment of the following indications (not an all-inclusive list) because its effectiveness for these indications has not been established.

- Anal squamous cell carcinoma
- Bladder cancer
- Breast cancer
- Carcinosarcoma of endometrial, fallopian tube, or ovarian origin
- Diabetic macular edema
- Glioblastoma
- Melanoma
- Non-small-cell lung cancer
- Ovarian cancer
- Pancreatic cancer
- Prostate cancer
- Renal cell cancer
- Retinal vein occlusion
- Small-cell lung cancer
- Uterine leiomyosarcoma

Note: * Precertification of ziv-aflibercept (Zaltrap) is required of all Aetna participating providers and members in applicable plan designs. For precertification of ziv-aflibercept (Zaltrap), call (866) 503-0857, or fax (866) 267-3277.
Note: The recommended dosage of ziv-aflibercept (Zaltrap) is 4 mg/kg body weight as an intravenous infusion every 2 weeks.

See also CPB 0701 - Vascular Endothelial Growth Factor Inhibitors for Ocular Neovascularization.

Background

Ziv-aflibercept (formerly known as aflibercept, VEGF Trap) is a recombinant fusion protein, which acts as a soluble receptor that binds to vascular endothelial growth factor-A (VEGF-A), VEGF-B and placental growth factor (PIGF). Ziv-aflibercept is designed to act as a VEGF trap to prevent activation of VEGF receptors and thus inhibit angiogenesis. Inhibition of these factors can result in decreased neo-vascularization and decreased vascular permeability.

On August 3, 2012, the Food and Drug Administration (FDA) approved ziv-aflibercept (Zaltrap) for use in combination with a FOLFIRI (folinic acid, fluorouracil and irinotecan) chemotherapy regimen for the treatment of adults with metastatic colorectal cancer (MCRC). Zaltrap’s safety and effectiveness was evaluated in a randomized clinical study (Van Cutsem et al, 2012) of 1,226 patients with MCRC whose cancer grew while receiving oxaliplatin-based combination chemotherapy, or whose cancer was removed by surgery but returned within 6 months after receiving oxaliplatin-based combination chemotherapy for post-surgery (adjuvant) treatment. Participants received treatment until their cancer progressed or side effects became unacceptable. The study was designed to measure overall survival (OS). Patients who were assigned to receive the Zaltrap plus FOLFIRI combination (n = 612) lived an average of 13.5 months compared to an average of 12 months for those receiving FOLFIRI plus placebo (n = 614). A reduction in tumor size occurred in 20% of patients receiving the Zaltrap plus FOLFIRI combination versus 11% for those receiving FOLFIRI plus placebo. In addition, the clinical trial demonstrated an improvement in progression-free survival (PFS). The PFS for patients receiving the Zaltrap plus FOLFIRI combination was 6.9 months compared with 4.7 months for those receiving FOLFIRI plus placebo. Zaltrap is approved with a “Boxed Warning” alerting patients and health care professionals that the drug can cause severe and sometimes fatal bleeding, including gastro-intestinal (GI) bleeding. The most common adverse events (AEs) observed in patients receiving Zaltrap plus FOLFIRI were abdominal pain, decreased appetite, diarrhea, fatigue, headache, hypertension, leukopenia, proteinuria, stomatitis, and weight loss.

In a phase II clinical and pharmacokinetic study, Tang et al (2012) evaluated the safety and effectiveness of aflibercept in patients with MCRC who had received at least 1 prior palliative regimen. A total of 75 patients were enrolled onto this 2-stage phase II trial in 2 cohorts, bevacizumab naïve (n = 24) and prior bevacizumab (n = 51). Aflibercept was administered at 4 mg/kg intravenous 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 patients. In the prior bevacizumab cohort, 1 patient achieved a partial response and 6 patients had stable disease for 16 weeks or more. The median PFS in the bevacizumab-naïve and prior bevacizumab cohorts was 2 months (95% confidence interval [CI]: 1.7 to 8.6 months) and 2.4 months (95% CI: 1.9 to 3.7 months), respectively. Median OS was 10.4 months.
(95 % CI: 7.6 to 15.5) and 8.5 months (95 % CI: 6.2 to 10.6), respectively. The most common grade 3 or higher treatment-related AEs were hypertension, proteinuria, fatigue, and headache; 10 patients 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 patients with pre-treated MCRC with moderate toxicity.

Ziv-aflibercept has also been studied for other indications (e.g., bladder cancer, breast cancer, carcinosarcoma, diabetic macular edema, melanoma, non-small-cell lung cancer [NSCLC], ovarian cancer, pancreatic cancer, prostate cancer, and uterine leiomyosarcoma). However, there is insufficient evidence to support the use of ziv-aflibercept for these conditions.

In a multi-center, phase II study, Tarhini et al (2011) examined the effects of aflibercept in patients with inoperable stage III or stage IV melanoma of cutaneous or uveal origin and no prior chemotherapy. A 2-stage design was adopted to evaluate 4-month PFS rate (PFSR) and response rate. Aflibercept was given at 4 mg/kg intravenously every 2 weeks. Response was assessed every 8 weeks. First-stage accrual of 21 patients was specified and with an adequate 4-month PFSR accrual continued to a total of 41. Forty-one patients of aged 23 to 84 years (median = 57) were enrolled. Thirty-nine had American Joint Committee on Cancer stage IV (5 M1a, 7 M1b, and 27 M1c) and 2 had inoperable stage IIIC (N3). Eastern Cooperative Oncology Group (ECOG) performance status was 0 (27 patients) or 1 (14 patients). Ten patients had primary uveal melanoma, 28 cutaneous, and 3 had unknown primaries. A median of 7 cycles were initiated (range of 1 to 56). Grade 3 and 4 toxicities included hypertension in 9 patients (22 %) and proteinuria in 6 (15 %). Among 40 patients evaluable for efficacy (those who initiated aflibercept), 3 (7.5 %) had a confirmed partial response and 20 had PFS of 4 months or above. The predicted 1-year survival rate derived from the Korn meta-analysis model is 36 % (n = 39), whereas these investigators observed a corresponding 56.4 % survival rate at 1 year (95 % CI: 43 to 74, p < 0.005). Median OS in this trial was 16.3 months (95 % CI: 9.2 to “not reached”). These researchers observed a significant association between severity of hypertension following aflibercept and survival improvement. The authors concluded that aflibercept showed promising activity in patients with metastatic melanoma of cutaneous or uveal origin. They stated that further evaluation of aflibercept as a single-agent and in combination is warranted.

Zhu et al (2012) stated that the treatment of advanced urothelial cancer of the bladder has evolved substantially during recent years. Chemotherapy has been the mainstay of treatment and confers survival advantage. Despite such advances, the chemotherapy of bladder cancer is far from satisfactory due to severe side effects. Targeted therapy with novel drugs directed at specific molecular pathways opens promising new avenues to improve patient outcome. A systematic review examined the clinical data for novel targeted agents in 10 phase II clinical trials, with a focus on aflibercept, bevacizumab, gefitinib, lapatinib, sorafenib, sunitinib, and trastuzumab. Moreover, these researchers presented studies on other novel, promising targeted agents, including cetuximab, everolimus, and pazopanib. Although bevacizumab and trastuzumab have shown promising results for patients with advanced bladder cancer, other targeted agents have not achieved the same clinical benefit in this disease as seen in other common epithelial cancers. The authors stated that ultimately, combination targeted therapy, sequential therapy, adjuvant and neoadjuvant therapy may yield the best outcomes.
Perez and Spano (2012) stated that the success of endocrine therapies for hormone receptor-positive breast cancer and trastuzumab and lapatinib for targeting human epidermal growth factor receptor 2 (HER2)-positive tumors has paved the way for the clinical development of several other metastatic breast cancer (MBC)-targeted therapies. Although the benefit of bevacizumab in the MBC setting has become a topic of debate, clinical trial results are accumulating, and phase 3 evaluations are ongoing for newer HER2-targeted agents (pertuzumab and trastuzumab-maytansine immuno-conjugate) and VEGF-targeted agents (afibercept), as well as dual, epidermal growth factor receptor/HER2-targeted agents (afatinib [BIBW 2992] and neratinib), multi-targeted tyrosine kinase inhibitors (TKIs) (pazopanib and sunitinib), and mammalian target of rapamycin (everolimus) and poly (ADP-ribose) polymerase 1 inhibitors (iniparib, olaparib). These agents as well as other novel classes of anti-cancer agents are being tested in clinical trials with the potential of addressing unmet therapeutic needs in the MBC patient population.

In a phase II clinical study, Mackay et al (2012) examined the safety and effectiveness of single-agent aflibercept in women with gynecologic soft tissue sarcoma. Patients were enrolled in 2 cohorts each with Simon 2-stage designs: uterine leiomyosarcoma and carcinosarcoma of endometrial, fallopian tube, or ovarian origin. Eligibility criteria included less than or equal to 2 prior lines of chemotherapy for metastatic disease and ECOG performance status of less than or equal to 2. Aflibercept 4 mg/kg was administered intravenously on day 1 of a 14-day cycle. Primary endpoints were objective response and disease stabilization (PFS at 6 months). A total of 41 patients with uterine leiomyosarcoma and 22 patients with carcinosarcoma (19 uterine, 3 ovarian) were enrolled in this study. In the leiomyosarcoma cohort, 11 (27 %) patients had stable disease (SD), 4 with SD lasting at least 24 weeks. The 6-month PFS was 17 %, with median time to progression (TTP) of 1.8 (95 % CI:1.6 to 2.1) months. In the carcinosarcoma cohort, 2 (9 %) patients had SD, 1 lasting more than 24 weeks, median TTP was 1.6 months (95 % CI: 1.1 to 1.7). No partial responses were observed in patients from either cohort. Grade 3 or more aflibercept-related toxicity was uncommon and included abdominal pain, fatigue, headache, and hypertension. The authors concluded that single-agent aflibercept has modest activity in patients with uterine leiomyosarcoma and minimal activity in women with carcinosarcoma.

Stewart (2012) stated that aflibercept monotherapy significantly reduces tumor growth and extends survival in several orthotopic animal models, and has both prevented and reduced the growth of experimental choroidal neo-vascularization. Ongoing phase III trials are evaluating the effectiveness of aflibercept combined with chemotherapy in patients with advanced carcinomas. The phase III VELOUR trial determined that patients receiving aflibercept with irinotecan/5-fluorouracil as second line chemotherapy for MCRC experienced extended PFS and OS. Intra-vitreal aflibercept improved visual acuity in patients with exudative age-related macular degeneration and was non-inferior to standard therapy (ranibizumab). Ongoing phase III trials are investigating the use of aflibercept for diabetic macular edema and retinal vein occlusions.

In a double-blind, placebo-controlled, phase III clinical trial, Ramlau et al (2012) compared the effectiveness of ziv-aflibercept, with or without docetaxel in platinum-pretreated patients with advanced or metastatic non-squamous NSCLC. A total of 913 patients were randomly assigned to ziv-aflibercept 6 mg/kg intravenous (IV; n = 456) or IV placebo (n = 457), both administered every 3 weeks and in combination with docetaxel 75 mg/m². The primary end point was OS. Other efficacy outcomes, safety, and immunogenicity were
also assessed. Patient characteristics were balanced between arms; 12.3 % of patients had received prior bevacizumab. Ziv-aflibercept did not improve OS (hazard ratio [HR], 1.01; 95% CI: 0.87 to 1.17; stratified log-rank p = 0.90). The median OS was 10.1 months (95% CI: 9.2 to 11.6 months) for ziv-aflibercept and 10.4 months (95% CI: 9.2 to 11.9 months) for placebo. In exploratory analyses, median PFS was 5.2 months (95% CI: 4.4 to 5.6 months) for ziv-aflibercept versus 4.1 months (95% CI: 3.5 to 4.3 months) for placebo (HR, 0.82; 95% CI: 0.72 to 0.94; p = 0.0035); overall response rate was 23.3% of evaluable patients (95% CI: 19.1% to 27.4%) in the ziv-aflibercept arm versus 8.9% (95% CI: 6.1% to 11.6%; p < 0.001) in the placebo arm. Grade greater than or equal to 3 adverse events occurring more frequently in the ziv-aflibercept arm versus the placebo arm were neutropenia (28.0% versus 21.1%, respectively), fatigue (11.1% versus 4.2%, respectively), stomatitis (8.8% versus 0.7%, respectively), and hypertension (7.3% versus 0.9%, respectively). The authors concluded that the addition of ziv-aflibercept to standard docetaxel therapy did not improve OS.

Teoh and Secord (2012) provided an overview of angiogenesis, including the rationale for targeting angiogenesis as a treatment strategy for epithelial ovarian cancer (EOC) and discussed available clinical trial data with anti-angiogenic agents in EOC. These researchers stated that several therapies that target angiogenesis-specific pathways are undergoing clinical development for EOC. Although some of these agents have demonstrated single-agent activity for EOC, there is considerable interest in combining this treatment strategy with chemotherapy in an effort to potentially improve treatment benefits in this patient population. Bevacizumab is the most studied anti-angiogenic agent in EOC and has shown efficacy as monotherapy and combined with chemotherapy in both the relapsed/recurrent and first-line settings. However, results from recent phase 3 trials raise questions regarding patient selection and optimal dose, schedule, and duration of bevacizumab therapy. Other agents in various phases of testing include aflibercept; multi-ligand targeted anti-angiogenic TKIs (e.g., cediranib, pazopanib, sorafenib); and AMG 386, a selective angiopoietin inhibitor. The authors concluded that results from recently completed and ongoing clinical trials combining anti-angiogenic agents with chemotherapy are awaited in hopes of expanding therapeutic options for patients with EOC.

Gaya and Tse (2012) noted that aflibercept inhibits VEGF-induced angiogenesis in pre-clinical models. In tumor models, aflibercept is associated with the reduction of tumor vasculature and size, and the inhibition of ascites formation. Clinical studies are investigating the use of aflibercept alone and in combination with other anti-neoplastic therapies for the treatment of various cancers. Phase I and II studies have provided proof of principle, and support the continuing clinical investigation of aflibercept. Results from the phase III study, VITAL, of aflibercept in the second-line setting in patients with advanced NSCLC demonstrated efficacy in PFS and overall objective response rate, but OS was not significantly improved. The phase III VANILLA trial in metastatic pancreatic cancer showed no improvement in OS.

Agarwal et al (2012) reviewed the next generation of molecular targets in metastatic castration-resistant prostate cancer (mCRPC). Medline databases were searched for greater than 100 original articles published as of October 18, 2011, with the search terms metastatic castration-resistant prostate cancer, targeted therapy, biologic agents, and immunotherapy. Proceedings from the last 5 years of conferences of the American Society of Clinical Oncology, American Urological Association, European Society of Medical Oncology, and the European Association of Urology were also searched. These investigators included novel and promising drugs that have reached clinical trial
evaluation. The major findings were addressed in an evidence-based fashion. Prospective trials and important pre-clinical data were analyzed. The authors concluded that mCRPC is a disease with multiple molecular drivers. Molecular pathways being targeted in ongoing phase III trials are androgen signaling (MDV3100, TAK700), immuno-regulatory pathways (ipilimumab, Prostvac-VF-TRICOM), Src (dasatinib), Met (cabozantinib), clusterin (custirsen), and angiogenesis (aflibercept, tasquinimod).

Wilson et al (2013) reviewed key clinical issues underlying the assessment of in-vivo efficacy when using anti-angiogenic therapies for cancer treatment. These investigators noted that multi-ligand targeted anti-angiogenic therapies, such as ziv-aflibercept, are currently undergoing clinical evaluation. Ziv-aflibercept forms monomeric complexes with VEGF-A, VEGF-B, and PIGF, which have a long half-life, allowing optimization of ziv-aflibercept doses and angiogenic blockage. The authors concluded that although anti-angiogenic therapies have increased therapeutic options for cancer patients, their use is limited by a lack of established and standardized methodology to evaluate their efficacy in-vivo.

Sharma et al (2013) noted that the FDA has recently approved aflibercept for the treatment of CRC. These researchers reviewed pre-clinical and clinical data on the use of aflibercept alone and in combination with chemotherapy for the treatment of breast cancer, glioblastoma, NSCLC, ovarian cancer, pancreatic cancer, and renal cell cancer.

In a single-arm, multi-center, phase II study, Chen et al (2014) evaluated the safety and effectiveness of ziv-aflibercept in combination with cisplatin and pemetrexed in NSCLC. This trial enrolled patients with previously untreated, locally advanced or metastatic non-squamous NSCLC. Patients received intravenous ziv-aflibercept 6 mg kg(-1), pemetrexed 500 mg m(-2), and cisplatin 75 mg m(-2), every 21 days for up to 6 cycles. Maintenance administration of ziv-aflibercept was to continue until disease progression, intolerable toxicity or other cause for withdrawal. The co-primary end-points were objective response rate (ORR) and PFS; planned sample size was 72 patients. The study was closed prematurely because of 3 confirmed and 2 suspected cases of reversible posterior leukoencephalopathy syndrome (RPLS). A total of 42 patients were enrolled. Median age was 61.5 years; 55 % were male, 86 % Caucasian and 50 % had ECOG performance status = 0. A median of 4 cycles of ziv-aflibercept was administered. The most common treatment-emergent adverse events (TEAEs) of any grade were nausea (69 %) and fatigue (67 %), with hypertension (36 %) as the most common grade 3/4 TEAE. Of the 38 evaluable patients, ORR was 26 % and median PFS was 5 months. The authors concluded that cases of RPLS had been observed in other studies in the ziv-aflibercept clinical development program, but the rate observed in this study was higher than previously observed. This might be related to declining renal function and/or hypertension. Although ORR and PFS were in accordance with most historical first-line NSCLC studies, this combination of ziv-aflibercept/cisplatin/pemetrexed will not be further explored in NSCLC.

In a randomized, phase II clinical trial, Allen et al (2014) examined the effects of weekly topotecan with or without ziv-aflibercept (VEGF-trap) in patients with platinum-treated small-cell lung cancer (SCLC). Patients with previously treated SCLC (one line of platinum-based chemotherapy), performance status of 0 to 1, adequate organ function, treated brain metastases, and no recent vascular events or bleeding diatheses were eligible. Eligible patients were stratified as platinum-sensitive or platinum-refractory and randomly assigned to receive weekly topotecan 4 mg/m(2) intravenously (IV) with or without ziv-aflibercept 6
mg/kg IV every 21 days. Progression-free survival at 3 months was the primary end-point. In 189 randomly assigned patients, treatment arms were well-balanced with regard to clinical characteristics. The 3-month PFS was significantly improved with the addition of ziv-aflibercept in patients who had platinum-refractory disease (27 % versus 10 %; p = 0.02) but not in patients with platinum-sensitive disease (24 % versus 15 %; p = 0.22). Although response rate was low, disease control rate was higher with combination therapy than with topotecan alone in patients who had platinum-sensitive disease (37 % versus 18 %; p = 0.05) and in those who had platinum-refractory disease (25 % versus 15 %; p = 0.14). Overall survival was not significantly improved in either strata. Grades 3 to 5 toxicities were more common with the addition of ziv-aflibercept. The authors concluded that ziv-aflibercept improved the 3-month PFS in patients who had platinum-refractory SCLC, but its addition increased toxicity; OS was similar with combined ziv-aflibercept and topotecan compared with topotecan in both strata.

NCCN guidelines state that small intestine and appendiceal adenocarcinoma may be treated with systemic chemotherapy according to NCCN guidelines for colon cancer. NCCN guidelines for anal carcinoma state that anal adenocarcinoma is managed with NCCN guidelines for rectal cancer.

Appendix

Guidelines from the National Comprehensive Cancer Network (NCCN, 2014) recommend ziv-aflibercept for colorectal cancer in persons who meet the following indications:

- Used as therapy after first progression of unresectable advanced or metastatic disease in combination with irinotecan or with FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen for disease not previously receiving irinotecan-based regimens;
- or
- Therapy for persons with unresectable metachronous metastases and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen.

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

96401 - 96450

HCPCS codes covered if selection criteria are met:

J9400 Injection, ziv-aflibercept, 1 mg

Other HCPCS codes related to the CPB:

J0640 Injection, leucovorin calcium, per 50 mg [folinic acid]
J0641 Injection, levoleucovorin calcium, 0.5 mg
J9190 Injection, fluorouracil, 500 mg
J9206 Injection, irinotecan, 20 mg
J9263 Injection, oxaliplatin, 0.5 mg
Q0083 - Q0085 Chemotherapy administration

ICD-9 codes covered if selection criteria are met:
153.0 - 153.9 Malignant neoplasm of colon
154.0 - 154.8 Malignant neoplasm of rectum, rectosigmoid junction, and anus

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):
157.0 - 157.9 Malignant neoplasm of pancreas
162.2 - 162.9 Malignant neoplasm of lung [non-small-cell]
172.0 - 172.9 Malignant melanoma of skin
174.0 - 174.9 Malignant neoplasm of female breast
175.0 - 175.9 Malignant neoplasm of male breast
182.0 - 182.8 Malignant neoplasm of body of uterus
183.0 Malignant neoplasm of ovary
183.2 Malignant neoplasm of fallopian tube
185 Malignant neoplasm of prostate
188.0 - 188.9 Malignant neoplasm of bladder
189.0 - 189.1 Malignant neoplasm of kidney
191.0 - 191.9 Malignant neoplasm of brain [glioblastoma]
362.07 Diabetic macular edema
362.30 - 362.37 Retinal vascular occlusion

Other ICD-9 codes related to the CPB:
V58.11 - Encounter for antineoplastic chemotherapy and immunotherapy
V58.12

The above policy is based on the following references:


