09-J1000-80

Original Effective Date: 12/15/12

Reviewed: 01/09/19

Revised: 02/15/19

Subject: Ziv-aflibercept (Zaltrap®) IV

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Colorectal cancer is the fourth most frequently diagnosed cancer and the second most frequent cause of cancer death in the United States. Current treatment of metastatic colorectal cancer involves various agents used either alone or in combination, including bevacizumab, capecitabine, irinotecan, oxaliplatin, panitumumab, regorafenib, ziv-aflibercept, or 5-fluorouracil/leucovorin.

Ziv-aflibercept (Zaltrap®) was approved by the U.S. Food and Drug Administration (FDA) on August 3, 2012 for use in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI) in metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen. Ziv-aflibercept inhibits angiogenesis by binding to vascular endothelial growth factor (VEGF)-A, VEGF-B, and placental growth factors 1 and 2.

Aflibercept (ziv-aflibercept in the United States) was assessed in combination with FOLFIRI in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. The combination significantly improved overall survival as compared to FOLFIRI alone (hazard ratio [HR], 0.817) with median survival times of 13.5 versus 12 months, respectively. Progression-free survival was also significantly improved (HR, 0.758) with median survival times of 6.9 versus 4.67 months, respectively.

POSITION STATEMENT:

I. Initiation of ziv-aflibercept (Zaltrap®) **meets the definition of medical necessity** for members diagnosed with **ANY** of the following conditions when ALL associated criteria are met:

A. **Colon or rectal cancer**

1. Use is for **ONE** of the following:
    a. Primary treatment in members with unresectable metachronous metastases who received previous adjuvant FOLFOX (flurouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months
    b. Subsequent therapy in member's with unresectable advanced or metastatic disease after first disease progression on **ONE** of the following:
        i. Oxaliplatin (e.g. FOLFOX, CapeOX)
        ii. 5-fluorouracil/leucovorin
        iii. Capecitabine
2. Member has not previously received therapy with irinotecan
3. Use will be in combination with **ONE** of the following:
    a. FOLFIRI (5-fluorouracil, leucovorin, irinotecan)
    b. irinotecan
4. The dose does not exceed 4 mg/kg every 2 weeks

B. **Other FDA-approved or NCCN supported diagnosis** (not previously listed above)

1. **ONE** of the following is met:
    a. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
    b. Indication AND usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
2. Dose does not exceed the maximum FDA-approved dose

Duration of approval: 6 months

II.Continuation of ziv-aflibercept (Zaltrap®) meets the definition of medical necessity for colon or rectal cancer, or other FDA-approved or NCCN supported diagnosis when the following criteria are met:

A. The member's disease has not progressed while receiving treatment with ziv-aflibercept
B. The member has been previously approved by Florida Blue or another health plan in the past 2 years, OR the member has previously met all indication-specific criteria for coverage
C. The dose does not exceed 4 mg/kg every 2 weeks

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

4 mg/kg as an intravenous infusion over 1 hour every 2 weeks

Drug Availability

100 mg/4 mL (25 mg/mL), 200 mg/8 mL (25 mg/mL) single-use vials

PRECAUTIONS:

Boxed Warning

- Hemorrhage: Severe and sometimes fatal hemorrhage, including gastrointestinal (GI) hemorrhage, has been reported. Do not administer in patients with severe hemorrhage.
- Gastrointestinal Perforation: Discontinue if patient experiences perforation.
- Compromised Wound Healing: Suspend for at least 4 weeks prior to elective surgery, and do not resume for at least 4 weeks following major surgery and until the surgical wound is fully healed.

Contraindications

None

Precautions/Warnings

- Fistula Formation: Discontinue if fistula occurs.
- Hypertension: Monitor blood pressure and treat hypertension. Suspend temporarily if hypertension is not controlled. Discontinue if hypertensive crisis develops.
- Arterial Thromboembolic Events (e.g. transient ischemic attacks, cerebrovascular accident, angina pectoris). Discontinue if arterial thromboembolic events occur.
- Proteinuria: Monitor urine protein. Suspend use when proteinuria is greater than or equal to 2 grams in 24 hours. Discontinue if nephrotic syndrome or thrombotic microangiopathy develops.
- Neutropenia and Neutropenic Complications: Delay administration until neutrophil count is greater than or equal to 1.5 x 109/L.
- Diarrhea and Dehydration: Incidence of severe diarrhea and dehydration is increased and elderly patients should be monitored closely.
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Discontinue use if RPLS occurs.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9400	Injection, ziv-aflibercept, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity:

C17.0 – C17.2	Malignant neoplasm of small intestine including duodenum, jejunum and ileum
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0 – C18.9	Malignant neoplasm of colon

C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C78.00 – C78.02	Secondary malignant neoplasm of unspecified lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

None

RELATED GUIDELINES:

Bevacizumab (Avastin®) Injection, 09-J0000-66

Capecitabine (Xeloda®) Tablets, 09-J1000-42

Human EGFR Inhibitors (cetuximab; panitumumab) IV, 09-J0000-94

Irinotecan HCl (Camptosar®) IV, 09-J0000-99

Oxaliplatin (Eloxatin®) IV, 09-J1000-00

Ramucirumab (Cyramza™) Injection, 09-J2000-14

Regorafenib (Stivarga®) IV, 09-J1000-83

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/09/19.

GUIDELINE UPDATE INFORMATION:

12/15/12	New Medical Coverage Guideline.
01/01/14	Revision to guideline; consisting of code update.
01/15/14	Review and revision to guideline; consisting of revising and reformatting description, position statement, dosage/administration, precautions/warning, exceptions and references.
01/15/15	Review and revision to guideline; consisting of updating references.
11/01/15	Revision: ICD-9 Codes deleted.
01/15/16	Review and revision to guideline; consisting updating description, position statement, warnings, coding and references.
01/15/17	Review and revision to guideline; consisting updating position statement and references.
01/15/18	Review and revision to guideline; consisting updating position statement and references.
02/15/19	Review and revision to guideline; consisting updating position statement and references.