Clinical Policy: Ziv-Aflibercept (Zaltrap)

Reference Number: CP.PHAR.325
Effective Date: 03/17
Last Review Date: 03/17

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for ziv-aflibercept for injection (Zaltrap®).

Policy/Criteria
It is the policy of health plans affiliated with Centene Corporation® that Zaltrap is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Colorectal Cancer (must meet all):

1. Diagnosis of colorectal cancer (CRC);
2. Meets a or b:
   a. FDA approved use (i and ii):
      i. For metastatic CRC (mCRC) as subsequent therapy in combination with FOLFIRI*;
      ii. Disease is resistant to or has progressed following an oxaliplatin-containing regimen;
   b. Off-label NCCN recommended use (i or ii):
      i. As primary therapy:
         a) For unresectable metastases and previous adjuvant** FOLFOX* or CapeOX* therapy within the past 12 months (1 or 2):
            1) In combination with irinotecan;
            2) In combination with FOLFIRI*;
      ii. As subsequent therapy (a and b):
         a) After first progression of unresectable advanced or metastatic disease;
         b) In combination with irinotecan or FOLFIRI* for disease not previously treated with irinotecan-based therapy;
3. Member does not have a current grade 3† (severe) or grade 4† (life-threatening) hemorrhage (e.g., gastrointestinal hemorrhage, hematuria, post-procedural hemorrhage, intracranial hemorrhage, pulmonary hemorrhage/hemoptysis).

**FOLFIRI (fluorouracil, leucovorin, irinotecan); FOLFOX (fluorouracil, leucovorin, oxaliplatin); CapeOX (capecitabine and oxaliplatin).*
***Adjuvant therapy (therapy administered after the main treatment to help decrease the risk of cancer recurring).*
†Grading is based on the Common Terminology Criteria for Adverse Events (CTCAE).

Approval duration: 3 months

B. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy.

II. Continued Approval

A. Colorectal Cancer (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member has none of the following reasons to discontinue:
   a. Disease progression or unacceptable toxicity;
   b. Grade 3* (severe) or grade 4* (life-threatening) hemorrhage (e.g., gastrointestinal hemorrhage, hematuria, post-procedural hemorrhage, intracranial hemorrhage, pulmonary hemorrhage/hemoptysis);
   c. Gastrointestinal perforation;
   d. Compromised wound healing;
   e. Fistula formation (e.g., anal, enterovesical, enterocutaneous, colovaginal, intestinal sites);
   f. Hypertensive crisis or hypertensive encephalopathy;
   g. Arterial thromboembolic event (e.g., transient ischemic attack, cerebrovascular accident, angina pectoris);
   h. Nephrotic syndrome (i.e., heavy proteinuria, hypoalbuminemia, and peripheral edema;
   i. Thrombotic microangiopathy (i.e., microvascular thrombosis);
   j. Reversible posterior leukoencephalopathy syndrome.

**Grading is based on the Common Terminology Criteria for Adverse Events (CTCAE).*

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy; or
2. Refer to CP.PHAR.57 - Global Biopharm Policy**.**

Background

Description/Mechanism of Action:
Zaltrap is a recombinant fusion protein acting as a soluble receptor that binds to human VEGF-A, to human VEGF-B, and to human PIGF. By binding to these endogenous ligands, ziv-aflibercept can inhibit the binding and activation of their cognate receptors. This inhibition can result in decreased neovascularization and decreased vascular permeability. In animals, ziv-aflibercept was shown to inhibit the proliferation of endothelial cells, thereby inhibiting the growth of new blood vessels. Ziv-aflibercept inhibited the growth of xenotransplanted colon tumors in mice.

Formulations:
Zaltrap is supplied in 5 mL and 10 mL vials containing ziv-aflibercept at a concentration of 25 mg/mL:

- Carton containing one single-use vial of 100 mg per 4 mL (25 mg/mL)
- Carton containing three single-use vials of 100 mg per 4 mL (25 mg/mL)

- Carton containing one single-use vial of 200 mg per 8 mL (25 mg/mL)

FDA Approved Indications:
Zaltrap is a vascular endothelial growth factor (VEGF) inhibitor/intravenous formulation indicated for:

- Metastatic colorectal cancer (mCRC), that is resistant to or has progressed following an oxaliplatin-containing regimen, in combination with 5-fluorouracil, leucovorin, irinotecan (FOLFIRI).

Appendices

Appendix A: Abbreviation Key

CapeOX: Capecitabine and oxaliplatin
CRC: Colorectal cancer
CTCAE: Common terminology criteria for adverse events
FOLFIRI: Fluorouracil, leucovorin, irinotecan
FOLFOX: Fluorouracil, leucovorin, oxaliplatin
mCRC: Metastatic colorectal cancer
PIGF: Phosphatidylinositol glycan anchor biosynthesis class F
VEGF: Vascular endothelial growth factor

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9400	Injection, ziv-aflibercept, 1 mg

Reviews, Revisions, and Approvals	Date	Approval Date
Policy split from CP.PHAR.182 Excellus Oncology. NCCN off-label recommended uses added.	01/17	03/17

References

1. Zaltrap prescribing information. Bridgewater, NJ: Sanofi-Aventis U.S., LLC; June 2016. Available at http://products.sanofi.us/zaltrap/Zaltrap.pdf. Accessed January 25, 2017.
2. Ziv-aflibercept. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed January 25, 2017.
3. Colon cancer (Version 1.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 25, 2017.
4. Rectal cancer (Version 2.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 25, 2017.
5. KDIGO clinical practice guideline for glomerulonephritis. *Kidney International Supplements*. June 2012; 2(2): 139-274. Available at http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-GN-Guideline.pdf. Accessed January 26, 2017.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.