CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Ziv-aflibercept (Zaltrap®)

Version: 1.0

EFFECTIVE DATE: 1/1/2024

NantHealth® | Eviti®

Please note the following:

Ziv-aflibercept (Zaltrap®)

Note: For Medicare members/enrollees, 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. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within 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.

Ziv-aflibercept (Zaltrap): Discussion

Angiogenesis, or new blood vessel formation, has long been known to be a critical component of tumorigenesis. Ziv-aflibercept is a human recombinant fusion protein with antiangiogenic effects that functions as a decoy receptor to bind vascular endothelial growth factors A and B and placental growth factor. [1]

Ziv-aflibercept is approved by the Food and Drug Administration (FDA) in combination with fluorouracil, leucovorin, irinotecan (FOLFIRI), for the treatment of patients with metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen. [2]

The National Comprehensive Cancer Network (NCCN) endorses ziv-aflibercept in the following cancer types: colon and rectal. [3,4]

Ziv-aflibercept: Definitions

- **Deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H)** - When the microsatellite DNA segments in cancer cells show changes (mutations), this indicates that the tumor cells are deficient in the repair of the mismatch errors. These cancers have microsatellite instability (also called MSI-High, MSI-H, or mismatch repair deficiency, dMMR).
- **Food and Drug Administration (FDA) -** The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **National Comprehensive Cancer Network (NCCN) -** An alliance of 32 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.

- **Proficient mismatch repair/microsatellite-stable (pMMR/MMS) -** When microsatellite DNA segments are unchanged (not mutated), the tumor cells are considered microsatellite stable (MSS) or have proficient mismatch repair. MSS cancers have normal levels of mismatch repair gene and protein expression and are able to correct DNA mismatch repair errors proficiently.
- **Vascular endothelial growth factor (VEGF) -** A potent angiogenic factor that was first described as an essential growth factor for vascular endothelial cells. VEGF is up-regulated in many tumors.

Ziv-aflibercept: Policy

Ziv-aflibercept will be considered for coverage when the following criteria are met:

Colon Cancer (Adenocarcinoma)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Adjuvant treatment in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) or irinotecan for unresectable metachronous metastases for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, or ineligible for, or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) that converted to resectable disease after initial treatment; OR
4. Initial treatment for patients with unresectable metachronous metastases in combination with irinotecan, or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, or deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H), and the patient is not a candidate for immunotherapy and received previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin), or CapeOX (capecitabine and oxaliplatin) within the past 12 months; OR
5. Subsequent therapy for progression of advanced or metastatic disease for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for, or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen in patients not previously treated with irinotecan-based therapy.

Note: Biologic therapy is only appropriate for the continuation of a favorable response from conversion therapy (therapy to convert unresectable to resectable disease).

Appendiceal (Adenocarcinoma)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Subsequent therapy for progression of advanced or metastatic disease for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for, or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen in patients not previously treated with irinotecan-based therapy [3]

Rectal Cancer (Adenocarcinoma)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Adjuvant treatment in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) or irinotecan for unresectable metachronous metastases for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, that converted to resectable disease after initial treatment; OR
4. Initial treatment for patients with unresectable metachronous metastases in combination with irinotecan, or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, and previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; OR
5. Subsequent therapy for progression of advanced or metastatic disease for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for, or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen in patients not previously treated with irinotecan-based therapy [4]

Note:

1. Biologic therapy is only appropriate for the continuation of a favorable response from conversion therapy (therapy to convert unresectable to resectable disease).
2. Coverage of ziv-aflibercept will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation, or when all criteria are met.

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Ziv-aflibercept: References

1. Aflibercept – A Decoy VEGF Receptor. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5145308. Accessed May 18, 2023.
2. Ziv-aflibercept (Zaltrap) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125418s047lbl.pdf. Accessed May 18, 2023.
3. National Comprehensive Cancer Network Guidelines. Colon Cancer (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed May 18, 2023.
4. National Comprehensive Cancer Network Guidelines. Rectal Cancer (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed May 18, 2023.

Ziv-aflibercept: Coding (CPT®, ICD 10 and HCPCS) *

* Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment.

CODE	DESCRIPTION
C18.2 – C19	Malignant neoplasm of the colon
C20	Malignant neoplasm of the rectum
J9400	Ziv-aflibercept (Zaltrap)

Ziv-aflibercept: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	6/1/2023
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	11/2/2023
6	Revision Changes:	