Medical Policy:

Zaltrap® (ziv-aflibercept) Intravenous

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.180	January 2, 2025	

The treating physician or primary care provider must submit to EmblemHealth, or ConnectiCare, as applicable (hereinafter jointly referred to as "EmblemHealth"), the clinical evidence that the member meets the criteria for the treatment or surgical procedure. Without this documentation and information, EmblemHealth will not be able to properly review the request preauthorization or post-payment review. The clinical review criteria expressed below reflects how EmblemHealth determines whether certain services or supplies are medically necessary. This clinical policy is not intended to pre-empt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Health care providers are expected to exercise their medical judgment in rendering appropriate care.

EmblemHealth established the clinical review criteria based upon a review of currently available clinical information (including clinical outcome studies in the peer reviewed published medical literature, regulatory status of the technology, evidence-based guidelines of public health and health research agencies, evidence-based guidelines and positions of leading national health professional organizations, views of physicians practicing in relevant clinical areas, and other relevant factors). EmblemHealth expressly reserves the right to revise these conclusions as clinical information changes and welcomes further relevant information. Each benefit program defines which services are covered. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered and/or paid for by EmblemHealth, as some programs exclude coverage for services or supplies that EmblemHealth considers medically necessary.

If there is a discrepancy between this guideline and a member's benefits program, the benefits program will govern. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test or procedure over another. In addition, coverage may be mandated by applicable legal requirements of a state, the Federal Government or the Centers for Medicare & Medicaid Services (CMS) for Medicare and Medicaid members. All coding and web site links are accurate at time of publication.

EmblemHealth may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. EmblemHealth Services Company, LLC, has adopted this policy in providing management, administrative and other services to EmblemHealth Plan, Inc., EmblemHealth Insurance Company, EmblemHealth Services Company, LLC, and Health Insurance Plan of Greater New York (HIP) related to health benefit plans offered by these entities. ConnectiCare, an EmblemHealth company, has also adopted this policy. All of the aforementioned entities are affiliated companies under common control of EmblemHealth Inc.

Definitions

Zaltrap (ziv-aflibercept): is an angiogenesis inhibitor. It is a fully humanized recombinant fusion protein that acts as a soluble receptor to bind vascular endothelial growth factor (VEGF)-A, VEGF-B, and placental growth factors 1 and 2, which prevents other native receptors from binding. Inhibition of native receptor binding can result in decreased neovascularization and decreased vascular permeability. In animals, ziv-aflibercept inhibited the growth of new blood vessels through inhibition of endothelial cell proliferation. Also, in mice, ziv-aflibercept inhibited the growth of xenotransplanted colon tumors.

Zaltrap (ziv-aflibercept), in combination with FOLFIRI, is FDA approved for the treatment of patients with metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing chemotherapy regimen.

Length of Authorization

Coverage will be provided for 6 months and may be renewed.

Dosing Limits [Medical Benefit]

Max Units (per dose and over time):

500 billable units per 14 days

Guideline

I. Initial Approval Criteria

Zaltrap *may be considered medically necessary if the below condition is met* ***AND*** *use is consistent with the medical necessity criteria that follows:*

1. **Colorectal Cancer (CRC) † ‡**
   - A. Patient is at least 18 years old; **AND**
   - B. Patient has not had any major surgeries in the previous 4 weeks prior to therapy; **AND**
   - C. Patient has metastatic disease that is resistant to or has progressed following an oxaliplatin-containing regimen (e.g., FOLFOX, CapeOX) †; **AND**
     - i. Used in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan); **OR**
   - D. Used as initial treatment for patients with unresectable metastases and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; **AND**
     - i. Used in combination with irinotecan or FOLFIRI; **AND**
     - ii. Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
   - E. Used as subsequent therapy for progression of advanced or metastatic disease; **AND**
     - i. Patient has not previously treated with irinotecan-based therapy; **AND**
     - ii. Used in combination with irinotecan or FOLFIRI; **AND**
       - a. Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
       - b. Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSIH) disease or polymerase epsilon/delta (POLE/POLD1) mutation; **AND**
         - 1.) Patient is not eligible for or has progressed on checkpoint inhibitor immunotherapy

2. **Appendiceal Adenocarcinoma ‡**
   - A. Used as subsequent therapy for progression of advanced or metastatic disease; **AND**
   - B. Patient has not previously been treated with irinotecan-based therapy or oxaliplatin; **AND**
   - C. Used in combination with irinotecan or FOLFIRI; **AND**
     - i. Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
     - ii. Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease or polymerase epsilon/delta (POLE/POLD1) mutation; **AND**
       - a. Patient is not eligible for or has progressed on checkpoint inhibitor immunotherapy

† FDA-Labeled Indication(s); **‡** Compendia Recommended Indication(s); **Φ** Orphan Drug

Limitations/Exclusions

Zaltrap is not considered medically necessary for when any of the following selection criteria is met:

1. Zaltrap (ziv-aflibercept) is not being used in members with any of the following:
   A. Non-metastatic disease
   B. Within 4 weeks prior to and 4 weeks following surgery and not until surgical wound is fully healed.
   C. Progression of disease while on Zaltrap (ziv-aflibercept) or restarted after progression of disease.
2. Dosing exceeds single dose limit of Zaltrap (ziv-aflibercept) 4mg/kg every 2 weeks.
3. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

II. Renewal Criteria

1. Patient continues to meet INITIAL APPROVAL CRITERIA; **AND**
2. Tumor response with disease stabilization or reduction of tumor size and spread; **AND**
3. Absence of unacceptable toxicity from the drug including hemorrhage, gastrointestinal perforation, fistula formation, hypertension, wound healing complications, arterial thromboembolic events, proteinuria, neutropenic complications, reversible posterior leukoencephalopathy syndrome (RPLS); severe diarrhea/dehydration, etc.

Dosage/Administration

Indication	Dose
All indications	4mg/kg administered as an intravenous infusion over 1 hour every 2 weeks.

Applicable Procedure Codes

Code	Description
J9400	Injection, ziv-aflibercept, 1 mg, 1 billable unit = 1 mg

Applicable NDCs

Code	Description
00024-5840-xx	Zaltrap 100 mg injection
00024-5841-xx	Zaltrap 200 mg injection

ICD-10 Diagnoses

Code	Description
C17.0	Malignant neoplasm duodenum
C17.1	Malignant neoplasm jejunum
C17.2	Malignant neoplasm ileum
C17.8	Malignant neoplasm of overlapping sites of small intestines
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm appendix
C18.2	Malignant neoplasm ascending colon

C18.3	Malignant neoplasm hepatic flexure
C18.4	Malignant neoplasm transverse colon
C18.5	Malignant neoplasm splenic flexure
C18.6	Malignant neoplasm descending colon
C18.7	Malignant neoplasm sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of large intestines
C18.9	Malignant neoplasm of colon, unspecified
C19.0	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	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.068	Personal history of other malignant neoplasm of small intestine

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	1/2/2025	Annual Review: Initial Criteria: Colorectal Cancer: changed the word “primary” to “initial” in the following statement: “Used as initial treatment for patients with unresectable metastases and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; AND” and Added: “Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; OR” Under subsequent therapy added: “a. Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; OR Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSIH) disease or polymerase epsilon/delta (POLE/POLD1) mutation; AND Patient is not eligible for or has progressed on checkpoint inhibitor immunotherapy” Added Appendiceal Adenocarcinoma indication and criteria
EmblemHealth & ConnectiCare	1/2/2024	Annual Review: Initial Criteria: Removed “Must be used in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen; AND i. Patient has metastatic disease that is resistant to or has progressed following an oxaliplatin-containing regimen; OR ii. Used as subsequent therapy for the treatment of unresectable advanced or metastatic disease in a patient who has not previously received irinotecan-based therapy”. Added: “C. Patient has metastatic disease that is resistant to or has progressed following an oxaliplatin containing regimen (e.g., FOLFOX, CapeOX) †; AND i. Used in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan); OR D. Used as primary treatment for patients with unresectable metastases and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; AND i. Used in combination with irinotecan or FOLFIRI; OR E. Used as subsequent therapy for progression of advanced or metastatic disease in patients not previously treated with

		irinotecan-based therapy; AND i. Used in combination with irinotecan or FOLFIRI" Limitations/Exclusions: Removed "As first line therapy without resistance to or has progressed following an oxaliplatin-based regimen or irinotecan-based regimen"
EmblemHealth & ConnectiCare	3/6/2023	Annual Review: No Revisions
EmblemHealth & ConnectiCare	10/13/2022	Transferred policy to new template
EmblemHealth & ConnectiCare	07/15/2019	Annual review

References

1. Zaltrap prescribing information. Sanofi-Aventis U.S. LLC, Bridgewater, NJ. 2016.
2. Clinical Pharmacology Elsevier Gold Standard. 2018.
3. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, Co. 2018.
4. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium. 2018.
5. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD. 2018.