Zaltrap® (ziv-aflibercept)
(Intravenous)

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I. Length of Authorization

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

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Zaltrap 100 mg/4 mL injection: 2 vials per 28 days
- Zaltrap 200 mg/8 mL injection: 4 vials per 28 days

B. Max Units (per dose and over time) [HCPCS Unit]:

- 500 billable units every 14 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Universal Criteria [1]

- Patient does not have recent history of severe hemorrhage; **AND**
- Ziv-aflibercept will be not administered for at least 4 weeks following major surgery; **AND**
- Patient does not have a surgical wound that has not fully healed; **AND**

Colorectal Cancer (CRC) † ‡ [1,2,6,8]

- Patient has metastatic disease that is resistant to or has progressed following an oxaliplatin-containing regimen (e.g., FOLFOX, CapeOX) †; **AND**
  - Used in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan); **AND**

- Use of ziv-aflibercept will be restricted to patients with a contraindication or intolerance to bevacizumab (or a commercially available bevacizumab biosimilar product); **OR**

- Used as initial treatment for patients with unresectable metastases; **AND**
  - Patient previously received FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; **AND**
  - Used in combination with irinotecan or FOLFIRI; **AND**
  - Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **AND**

- Use of ziv-aflibercept will be restricted to patients with a contraindication or intolerance to bevacizumab (or a commercially available bevacizumab biosimilar product); **OR**

- Used as subsequent therapy for progression of advanced or metastatic disease; **AND**
  - Patient has <u>not</u> been previously treated with irinotecan-based therapy; **AND**
  - Used in combination with irinotecan or FOLFIRI; **AND**

- Use of ziv-aflibercept will be restricted to patients with a contraindication or intolerance to bevacizumab (or a commercially available bevacizumab biosimilar product); **AND**

    - Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
    - Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease or polymerase epsilon/delta (POLE/POLD1) mutation; **AND**
      - Patient is not eligible for or has progressed on checkpoint inhibitor immunotherapy

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

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

IV. Renewal Criteria [1,2]

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the universal and indication-specific criteria as identified in section III; **AND**

- Disease response with treatment as defined by stabilization of disease or decrease in size or spread of tumor; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: hemorrhage, gastrointestinal perforation, fistula formation, uncontrolled hypertension (e.g., hypertensive crisis, hypertensive encephalopathy), impaired wound healing, arterial thromboembolic events, proteinuria (e.g., nephrotic syndrome, thrombotic microangiopathy, proteinuria ≥ 2g/24 hours), neutropenia and neutropenic complications, reversible posterior leukoencephalopathy syndrome (RPLS), severe diarrhea/dehydration, etc.

V. Dosage/Administration [1,2,8]

Indication	Dose
Colorectal Cancer	Administer 4 mg/kg of actual body weight as an intravenous (IV) infusion every two weeks, until disease progression or unacceptable toxicity.

VI. Billing Code/Availability Information

HCPCS Code:

- J9400 – Injection, ziv-aflibercept, 1 mg; 1 billable unit = 1 mg

NDC(s):

- Zaltrap 100 mg/4 mL solution, single-dose vial: 00024-5840 -xx
- Zaltrap 200 mg/8 mL solution, single-dose vial: 00024-5841 -xx

VII. References (STANDARD)

1. Zaltrap [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S. LLC; December 2023. Accessed April 2024.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) ziv-aflibercept. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2024.
3. Fahrenbruch R, Kintzel P, Bott AM, et al. Dose Rounding of Biologic and Cytotoxic Anticancer Agents: A Position Statement of the Hematology/Oncology Pharmacy Association. J Oncol Pract. 2018 Mar;14(3):e130-e136.
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5. Bach PB, Conti RM, Muller RJ, et al. Overspending driven by oversized single dose vials of cancer drugs. BMJ. 2016 Feb 29;352:i788.
6. Tabernero J, Paccard C, Chiron M, et al. Placental growth factor and the angiogenic environment based on analysis of baseline plasma biomarkers from the VELOUR trial. Journal of Clinical Oncology35, no. 4_suppl(February 01, 2017)592-592. DOI: 10.1200/JCO.2017.35.4_suppl.592.
7. Sanofi. A Multinational, Randomized, Double-blind Study, Comparing the Efficacy of Aflibercept Once Every 2 Weeks Versus Placebo in Patients With Metastatic Colorectal Cancer (MCRC) Treated With Irinotecan / 5-FU Combination (FOLFIRI) After Failure of an Oxaliplatin Based Regimen. Available from: https://clinicaltrials.gov/ct2/show/NCT00561470?term=NCT00561470&draw=2&rank=1. ClinicalTrials.gov Identifier: NCT00561470. Accessed January 2024.
8. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 1.2024. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2024.

VIII. References (ENHANCED)

1e. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) Rectal Cancer, Version 1.2024. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2024.
2e. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML 18147); a randomised phase 3 trial. Lancet Oncol 2013;14:29-37.
3e. Masi G, Salvatore L, Boni L, et al. Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized BEBYP trial. Ann Oncol 2015;26:724-730.
4e. Iwamoto S, Takahashi T, Tamagawa H, et al. FOLFIRI plus bevacizumab as second-line therapy in patients with metastatic colorectal cancer after first-line bevacizumab plus oxaliplatin-based therapy: the randomized phase III EAGLE study. Ann Oncol 2015;26:1427-1433.
5e. Cartwright TH, Yim YM, Yu E, et al. Survival outcomes of bevacizumab beyond progression in metastatic colorectal cancer patients treated in US community oncology. Clin Colorectal Cancer 2012;11:238-246.

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7e. Van Custem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 2012;30:3499-3506.

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10e. Goldstein DA, El-Rayes BF. Considering Efficacy and Cost, Where Does Ramucirumab Fit in the Management of Metastatic Colorectal Cancer? Oncologist 2015;20:981-982.

11e. Magellan Rx Management. Zaltrap Clinical Literature Review Analysis. Last updated April 2024. Accessed April 2024.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C18.0	Malignant neoplasm of cecum
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of large intestines
C18.9	Malignant neoplasm of colon, unspecified
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	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

ICD-10	ICD-10 Description
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
Z85.038	Personal history of other malignant neoplasm of large intestine

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC