Zaltrap® (ziv-aflibercept)
(Intravenous)

Document Number: IC-0161

Last Review Date: 09/04/2025
Date of Origin: 02/07/2013
Dates Reviewed: 12/2013, 03/2014, 06/2014, 09/2014, 12/2014, 03/2015, 05/2015, 08/2015, 11/2015, 02/2016, 05/2016, 08/2016, 11/2016, 02/2017, 05/2017, 08/2017, 11/2017, 2/2018, 5/2018, 09/2018, 12/2018, 03/2019, 06/2019, 9/2019, 12/2019, 03/2020, 06/2020, 09/2020, 03/2022, 03/2023, 03/2024, 09/2025

I. Length of Authorization

- Initial: Prior authorization validity will be provided initially for 6 months.
- Renewal: Prior authorization validity may be renewed every 6 months thereafter.

II. Dosing Limits

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

- 500 billable units every 14 days

III. Initial Approval Criteria [1]

Prior authorization validity 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); **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 with FOLFIRI; **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 with FOLFIRI

¥ *Note: NCCN recommends universal MMR or MSI testing in all newly diagnosed patients. If deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype (e.g., TMB>50 mut/Mb), treatment should include checkpoint inhibitor immunotherapy if the patient is a candidate.*

Appendiceal Adenocarcinoma – Colon Cancer ¥ ‡ [2]

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

¥ *Note: NCCN recommends universal MMR or MSI testing in all newly diagnosed patients. If deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype (e.g., TMB>50 mut/Mb), treatment should include checkpoint inhibitor immunotherapy if the patient is a candidate.*

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

IV. Renewal Criteria [1,2]

Prior authorization validity 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
All indications	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

1. Zaltrap [package insert]. Morristown, NJ; Sanofi-Aventis U.S. LLC; May 2025. Accessed August 2025.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) ziv-aflibercept. National Comprehensive Cancer Network, 2025. 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 August 2025.
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.
4. Hematology/Oncology Pharmacy Association (2019). *Intravenous Cancer Drug Waste Issue Brief*. Updated February 2024. Retrieved from: HOPA_Drug_Waste_Issue_Brief_-_Updated_02.22.24.pdf
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 4.2025. National Comprehensive Cancer Network, 2025. 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 August 2025.

Appendix A – Non-Quantitative Treatment Limitations (NQTL) Factor Checklist

Non-quantitative treatment limitations (NQTLs) refer to the methods, guidelines, standards of evidence, or other conditions that can restrict how long or to what extent benefits are provided under a health plan. These may include things like utilization review or prior authorization. The utilization management NQTL

applies comparably, and not more stringently, to mental health/substance use disorder (MH/SUD) Medical Benefit Prescription Drugs and medical/surgical (M/S) Medical Benefit Prescription Drugs. The table below lists the factors that were considered in designing and applying prior authorization to this drug/drug group, and a summary of the conclusions that Prime's assessment led to for each.

Factor	Conclusion
Indication	Yes: Consider for PA
Safety and efficacy	No: PA not a priority
Potential for misuse/abuse	No: PA not a priority
Cost of drug	Yes: Consider for PA

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
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
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 VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC