Zaltrap® (ziv-aflibercept)
(Intravenous)

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Document Number: MODA-0391

Last Review Date: 04/06/2021
Date of Origin: 09/03/2019
Dates Reviewed: 9/2019, 01/2020, 04/2020, 07/2020, 10/2020, 04/2021

I. Length of Authorization

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

II. Dosing Limits

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

- Zaltrap 100 mg injection: 2 vials per 28 days
- Zaltrap 200 mg 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 [1,2,6]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; AND

Colorectal Cancer † [1,2,6,10,15]

- Must be used in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen; AND
  - Used in one of the following treatment settings:
    - Patient has metastatic disease that is resistant to or has progressed following an oxaliplatin-containing regimen (e.g., FOLFOX, CapeOX) †; OR
    - Used as primary treatment for patients with unresectable metachronous metastases; AND
      - Patient received previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; OR

- Used as subsequent therapy for progression of advanced or metastatic disease in patients not previously treated with irinotecan-based therapy

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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)

IV. Renewal Criteria [1,2]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. 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 the following: hemorrhage, gastrointestinal perforation, fistula formation, uncontrolled hypertension, hypertensive crisis, hypertensive encephalopathy, wound healing complications, arterial thromboembolic events, proteinuria (≥2 g/24 hours), nephrotic syndrome, thrombotic microangiopathy (TMA), neutropenic complications, reversible posterior leukoencephalopathy syndrome (RPLS), severe diarrhea/dehydration, etc.

V. Dosage/Administration [1,2]

Indication	Dose
Colorectal cancer	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:

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

VII. References (STANDARD)

1. Zaltrap [package insert]. Bridgewater, NJ; Sanofi-Aventis U.S. LLC; December 2020. Accessed March 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) ziv-aflibercept. National Comprehensive Cancer Network, 2021. 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 March 2021.
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. Retrieved from http://www.hoparx.org/images/hopa/advocacy/Issue-Briefs/Drug_Waste_2019.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 2020.

VIII. References (ENHANCED)

1e. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) Colon Cancer, Version 2.2021. National Comprehensive Cancer Network, 2021. 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 March 2021.

2e. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) Rectal Cancer, Version 1.2021. National Comprehensive Cancer Network, 2021. 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 March 2021.

3e. 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.

4e. 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.

5e. 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.

6e. 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.

7e. Grothey A, Flick ED, Cohn AL, et al. Bevacizumab exposure beyond first disease progression in patients with metastatic colorectal cancer: analyses of the ARIES observational cohort study. Pharmacoepidemiol Drug Saf 2014;23:726-734.

8e. 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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11e. 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.

12e. Magellan Health, Magellan Rx Management. Zaltrap Clinical Literature Review Analysis. Last updated March 2021. Accessed March 2021.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C17.0	Malignant neoplasm duodenum

ICD-10	ICD-10 Description
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 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
Z85.068	Personal history of other malignant neoplasm of small intestine

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

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 Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered 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

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
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, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
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

Appendix 3 - CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate

Colorectal Cancer:

Colon Cancer – Subsequent Systemic Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Irinotecan + oxaliplatin based chemo + bevacizumab	2A preferred	YES, in combo with fluoropyrimidine-irinotecan or oxaliplatin based chemo as 2nd line in pts who progressed on 1st line Avastin Dosing: 5 mg/kg Q2 weeks or 7.5 mg/kg Q3 weeks	Phase 3 (ML18147), study evaluating continuation of bevacizumab after first progression in mCRC after standard 1st-line bevacizumab based tx	Irinotecan/Oxaliplatin based chemo	OS	Second Line	• Maintenance VEGF inhibition with bevacizumab plus standard 2nd-line chemo beyond dx progression has benefit in mCRC.
FOLFOX or FOLFIRI + bevacizumab	2A preferred	YES	Phase 3 (BEBYP), study to evaluate efficacy of continuing or reintroducing bevacizumab in combo with second-line chemo after progression to	FOLFOX or FOLFIRI	PFS	Second Line	• Continuation or the re-introduction of bevacizumab with second-line chemo beyond first progression improves the outcome

			bevacizumab-based first line tx				Comments: Study stopped premature out of consideration for the results of the ML18147 trial
FOLFIRI + bevacizumab	2A preferred	YES	Phase 3 (EAGLE), study to compare 2 doses of bevacizumab with FOLFIRI in 2nd line setting after 1st line therapy with bevacizumab plus oxaliplatin based tx	/	OS, TTF, safety	Second Line	• Bevacizumab 10 mg/kg plus FOLFIRI as second-line didn't prolong PFS compared to bevacizumab 5 mg/kg plus FOLFIRI in patients with mCRC.
Irinotecan + oxaliplatin based chemo + bevacizumab	2A preferred	YES	RETRO REVIEW, evaluation of the association between the continued use of bevacizumab beyond progression (BBP) and survival outcomes in mCRC pts in the community setting.	Irinotecan/Oxaliplatin based chemo	OS, post progression OS	Second Line	• BBP treatment is correlated with prolonged OS and ppOS in patients with mCRC.
Irinotecan + oxaliplatin based chemo + bevacizumab	2A preferred	YES	Observational cohort ARIES study analysis, examine association between exposure to bevacizumab after dx progression and post-progression survival in mCRC	/	PPS (post progression survival)	Second Line	• Analysis supports the observation that bevacizumab exposure after disease progression is associated with longer PPS in mCRC.
FOLFIRI (Irinotecan) + ziv-aflibercept	2A	YES, in combo with FOLFIRI in pts with mCRC that is resistant to or has progressed on an	Phase 3 (VELOUR), study of aflibercept w/FOLFIRI in mCRC pts previously tx with oxaliplatin and some with bevacizumab	FOLFIRI + placebo	OS	Second Line after a single prior oxaliplatin-containing regimen	• Aflibercept in combination with FOLFIRI conferred a statistically significant survival benefit over FOLFIRI combined with placebo in patients with mCRC previously treated with oxaliplatin. • Activity only when given in combo with FOLFIRI or in FOLFIRI naïve patients

		oxaliplatin regimen Dosing: 4 mg/kg Q2 weeks					
FOLFIRI (Irinotecan) + ziv-aflibercept	2A	YES	Phase 3 (VELOUR)-SUB-GROUP ANALYSIS, Aflibercept versus placebo in combination with FOLFIRI for tx of mCRC	FOLFIRI+ placebo	OS	Second Line after a single prior oxaliplatin-containing regimen	• Benefits of aflibercept in combo with FOLFIRI in pts with mCRC previously treated with oxaliplatin were maintained across the specific subgroups, including those with or without prior bevacizumab tx
FOLFIRI or Irinotecan + ramucirumab	2A	YES, in combo with FOLFIRI for the tx of mCRC with dx progression on or after prior tx with bevacizumab, oxaliplatin and fluoropyrimidine Dosing: 8 mg/kg Q2 weeks	Phase 3 (RAISE), study of ramucirumab + FOLIRI vs. placebo + FOLFIRI in patients with metastatic CRC that progressed during or after first-line therapy with bevacizumab, oxaliplatin and a fluoropyrimidine.	FOLFIRI + placebo	OS	Second Line	• Ramucirumab + FOLFIRI significantly improved IS compared to placebo + FOLFIRI as second line tx for metastatic CRC. • No unexpected AEs and toxicity was manageable. • Activity only when given in combo with FOLFIRI or in FOLFIRI naïve patients