Clinical Policy: Ziv-Aflibercept (Zaltrap)

Reference Number: PA.CP.PHAR.325
Effective Date: 01/2018
Last Review Date: 10/2023

Coding Implications
Revision Log

Description
Ziv-aflibercept (Zaltrap®) is a vascular endothelial growth factor (VEGF) inhibitor.

FDA Approved Indication(s)
Zaltrap, in combination with 5-fluorouracil, leucovorin, irinotecan (FOLFIRI), is indicated for patients with metastatic colorectal cancer (CRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

Policy/Criteria
It is the policy of PA Health & Wellness ® that Zaltrap is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Colorectal Cancer (must meet all):

1. Diagnosis of advanced, unresectable, or metastatic colorectal cancer (CRC);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Previous treatment with one of the following (a, b, c or d):
   a. An oxaliplatin-containing regimen (e.g., FOLFOX, CapeOX);
   b. A 5-fluorouracil and leucovorin-containing regimen (off-label);
   c. A capecitabine-containing regimen (off-label);
   d. Checkpoint inhibitor immunotherapy (e.g., Opdivo ± Yervoy, Keytruda, Jemperli) or ineligible to receive checkpoint inhibitor immunotherapy;
5. Prescribed in combination with irinotecan or FOLFIRI;
6. Request meets one of the following (a or b):
   a. Dose does not exceed 4 mg/kg every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

B. Other diagnoses/indications: Refer to PA.CP.PMN.53.

II. Continued Approval

A. Colorectal Cancer (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;
3. Request meets one of the following (a or b):
   a. Dose does not exceed 4 mg/kg every 2 weeks;

b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; or
2. Refer to PA.CP.PMN.53

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CapeOX: capecitabine and oxaliplatin
CRC: colorectal cancer
FDA: Food and Drug Administration
FOLFIRI: fluorouracil, leucovorin, irinotecan
FOLFOX: fluorouracil, leucovorin, oxaliplatin
VEGF: vascular endothelial growth factor

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Modified FOLFOX 6	Day 1: oxaliplatin 85 mg/m^2 IV Day 1: Folinic acid 400 mg/m^2 IV Days 1–3: 5-FU 400 mg/m^2 IV bolus on day 1, then 1,200 mg/m^2/day × 2 days (total 2,400 mg/m^2 over 46–48 hours) IV continuous infusion. Repeat cycle every 2 weeks.	See dosing regimen
CapeOX	Day 1: Oxaliplatin 130 mg/m^2 IV Days 1–14: Capecitabine 1,000 mg/m^2 PO BID. Repeat cycle every 3 weeks.	See dosing regimen
FOLFIRI	Day 1: Irinotecan 180 mg/m^2 IV Day 1: Leucovorin 400 mg/m^2 IV Day 1: Flurouracil 400 mg/m^2 IV followed by 2400 mg/m^2 continuous IV over 46 hours Repeat cycle every 14 days.	See dosing regimen
5-fluorouracil and leucovorin	Roswell Park regimen: Leucovorin 500 mg/m^2 IV followed by 5-FU 500 mg/m^2 IV bolus one hour after start of leucovorin on days 1, 8, 15, 22, 29, 36. Repeat every 8 weeks.	See dosing regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Biweekly regimen: Leucovorin 400 mg/m^2 IV on day one followed by 5-FU 400 mg/m^2 IV bolus then 1,200 mg/m^2 continuous IV. Repeat every 2 weeks. Weekly regimen: Leucovorin 20 mg/m^2 IV on day one followed 5-FU 500 mg/m^2 IV bolus one hour after start of leucovorin. Alternatively 5-FU 2,600 mg/m^2 continous IV with leucovorin 500 mg/m^2 IV. Repeat weekly.	
capecitabine	850 – 1,250 mg/m^2 PO BID on days 1-14. Repeat every 3 weeks.	2,500 mg/m^2/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

None reported

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CRC	4 mg/kg IV over 1 hour every two weeks	4 mg/kg

V. Product Availability

Single-use vial for injection: 100 mg/4 mL, 200 mg/8 mL

VI. References

1. Zaltrap Prescribing Information. Bridgewater, NJ: Sanofi-Aventis U.S., LLC; December 2020. Available at http://www.zaltrap.com/. Accessed July 7, 2023.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed July 7, 2023.
3. National Comprehensive Cancer Network. Colon Cancer Version 1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed July 7, 2023.
4. National Comprehensive Cancer Network. Rectal Cancer Version 1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed July 7, 2023.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9400	Injection, ziv-aflibercept, 1 mg

Reviews, Revisions, and Approvals	Date	Approval Date
4Q 2018 annual review: no significant changes; summarized NCCN and FDA-approved uses for improved clarity; added specialist involvement in care; references reviewed and updated	07/2018	
4Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020	10/2019	
4Q 2020 annual review: Added age limit; updated appendices; references reviewed and updated.	07/2020	
4Q 2021 annual review: no significant changes; references reviewed and updated	10/2021	
4Q 2022 annual review: added diagnosis qualifier that CRC is advanced, unresectable, or metastatic per NCCN; references reviewed and updated.	11/2022	
4Q 2023 annual review: no significant changes; references reviewed and updated.	10/2023	