Clinical Policy: Ziv-aflibercept (Zaltrap)

Reference Number: ERX.SPA.259
Effective Date: 12.01.18
Last Review Date: 11.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Zaltrap is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of CRC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Previous treatment with one of the following (a, b, or c):
   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);
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*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, or documentation supports that member is currently receiving Zaltrap for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):*

a. New dose does not exceed 4 mg/kg every 2 weeks;
b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. 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 2,400 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. 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:	See dosing regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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

V. Dosage and Administration

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

VI. Product Availability

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

VII. References

1. Zaltrap Prescribing Information. Bridgewater, NJ: Sanofi-Aventis U.S., LLC; December 2020. Available at http://www.zaltrap.com/. Accessed August 9, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 9, 2021.
3. National Comprehensive Cancer Network. Colon Cancer Version 2.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 9, 2021.
4. National Comprehensive Cancer Network. Rectal Cancer Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed August 9, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	08.07.18	11.18
4Q 2019 annual review: no significant changes; references reviewed and updated.	08.13.19	11.19
4Q 2020 annual review: no significant changes; references reviewed and updated.	07.23.20	11.20
4Q 2021 annual review: no significant changes; references reviewed and updated.	08.09.21	11.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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