Clinical Policy: Ziv-Aflibercept (Zaltrap)

Reference Number: PA.CP.PHAR.325
Effective Date: 01/18
Last Review Date: 10/30/2019

Coding Implications
Revision Log

Description
The intent of the criteria is to ensure that patients follow selection elements established by Pennsylvania Health and Wellness ® clinical policy for ziv-aflibercept for injection (Zaltrap®).

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 Pennsylvania Health and 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 colorectal cancer (CRC);
2. Prescribed by or in consultation with an oncologist;
3. 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);
4. Prescribed in combination with irinotecan or FOLFIRI;
5. 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 Pennsylvania Health and 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. 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).*

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Pennsylvania Health and 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

Background

Description/Mechanism of Action:

Zaltrap is a recombinant fusion protein acting as a soluble receptor that binds to human VEGF-A, to human VEGF-B, and to human PIGF. By binding to these endogenous ligands, ziv-aflibercept can inhibit the binding and activation of their cognate receptors. This inhibition can result in decreased neovascularization and decreased vascular permeability. In animals, ziv-aflibercept was shown to inhibit the proliferation of endothelial cells, thereby inhibiting the growth of new blood vessels. Ziv-aflibercept inhibited the growth of xenotransplanted colon tumors in mice.

Formulations:

Zaltrap is supplied in 5 mL and 10 mL vials containing ziv-aflibercept at a concentration of 25 mg/mL:

- Carton containing one single-use vial of 100 mg per 4 mL (25 mg/mL)
- Carton containing three single-use vials of 100 mg per 4 mL (25 mg/mL)
- Carton containing one single-use vial of 200 mg per 8 mL (25 mg/mL)

Appendices

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.	See dosing regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Repeat cycle every 2 weeks.	
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. 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.	See dosing regimen
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

- Contraindication(s): none reported
- Boxed warning(s): hemorrhage, gastrointestinal perforation, compromised wound healing

Appendix D: General Information

- NCCN Compendium include a Category 2A recommendation for Zaltrap as subsequent therapy for progression of unresectable advanced or metastatic disease in combination with irinotecan or with FOLFIRI regimen in patients not previously treated with irinotecan-based therapy.

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	07/18	
4Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020	10/30/19	

References

1. Zaltrap Prescribing Information. Bridgewater, NJ: Sanofi-Aventis U.S., LLC; June 2016. Available at http://www.zaltrap.com/. Accessed July 23, 2018.
2. Ziv-aflibercept. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed July 23, 2018.
3. Colon cancer (Version 2.2018). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed July 23, 2018.
4. Rectal cancer (Version 2.2018). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed July 23, 2018.