

Clinical Criteria

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| Subject: | Zaltrap (ziv-aflibercept) | | |
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Overview

This document addresses the use of Zaltrap (ziv-aflibercept). Zaltrap is a recombinant fusion protein consisting of vascular endothelial growth factor (VEGF)-binding portions that is primarily used to treat metastatic colorectal cancer.

The FDA approved indication for Zaltrap is, in combination with 5-fluorouracil, leucovorin, irinotecan (FOLFIRI), for treatment of metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen. The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for treatment of CRC. NCCN notes that no data exists that suggest activity of FOLFIRI plus Zaltrap in individuals who have progressed on FOLFIRI plus bevacizumab; FOLFIRI + Zaltrap has only shown activity when given to FOLFIRI-naïve individuals.

Within the guidelines, NCCN recommends that appendiceal adenocarcinoma be treated with chemotherapy according to colon cancer guidelines. Similarly, anal adenocarcinoma may be treated according to guidelines for rectal cancer.

In addition, NCCN notes that studies have shown that combination with more than one biologic agent is not associated with improved outcomes and can cause increased toxicity, specifically regarding the addition of Erbitux (cetuximab) or Vectibix (panitumumab) to a bevacizumab-containing regimen (Tol 2009, Hecht 2009). NCCN strongly recommends against the use of therapy involving concurrent combination of an anti-EGFR agent and an anti-VEGF agent.

Other Uses

NCCN also provides 2A recommendations for Zaltrap in combination with an irinotecan-based regimen for treatment of mCRC that has previously been treated with fluoro-pyrimidine without irinotecan **or** oxaliplatin. However, studies cited in this recommendation only investigated Zaltrap after previous treatment with an oxaliplatin-based regimen (Van Cutsem 2012).

Zaltrap has a black box warning for hemorrhage, gastrointestinal perforation, and compromised wound healing. Zaltrap should be discontinued in patients with severe hemorrhage, gastrointestinal perforation, and compromised wound healing. In addition, Zaltrap should be suspended for at least 4 weeks prior to elective surgery and not resumed for at least 4 weeks following major surgery and until surgical wound is fully healed.

Definitions and Measures

Adenocarcinoma: Cancer originating in cells that line specific internal organs and that have gland-like (secretory) properties.

Anal cancer: Cancer originating in the tissues of the anus; the anus is the opening of the rectum (last part of the large intestine) to the outside of the body.

Colon cancer: Cancer originating in the tissues of the colon (the longest part of the large intestine). Most colon cancers are adenocarcinomas that begin in cells that make and release mucus and other fluids.

Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).

Disease Progression: Cancer that continues to grow or spread.

Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

One line of therapy: Single line of therapy.

Progressive Disease (PD): Cancer that is growing, spreading, or getting worse.

Rectal cancer: Cancer originating in tissues of the rectum (the last several inches of the large intestine closest to the anus).

Refractory Disease: Illness or disease that does not respond to treatment.

Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Unresectable: Unable to be removed with surgery.

Vascular endothelial growth factor (VEGF): A substance made by cells that stimulates new blood vessel formation.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Zaltrap (ziv-aflibercept)

Requests for Zaltrap (ziv-aflibercept) may be approved if the following criteria are met:

- I. Individual has a diagnosis of metastatic colon, rectal, colorectal, ~~small-bowel~~, appendiceal, or anal adenocarcinoma (Label, NCCN 2A); **AND**
- I. The individual is resistant to or has disease progression following treatment with an oxaliplatin-containing regimen; **AND**
- II. Ziv-aflibercept will be used in combination with an irinotecan based regimen; **AND**
- III. Ziv-aflibercept will be given in a single line of therapy.

Requests for Zaltrap (ziv-aflibercept) may not be approved for the following:

- I. All other indications not included above; **OR**
- II. Ziv-aflibercept is given concomitantly with cetuximab, panitumumab, or bevacizumab (or bevacizumab biosimilar); **OR**
- III. Ziv-aflibercept is used in combination with the same irinotecan-based regimen that was previously used in combination with bevacizumab (or bevacizumab biosimilar).

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Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9400 Injection, ziv-aflibercept, 1 mg [Zaltrap]

ICD-10 Diagnosis

| | |
|--------------------|---|
| C18.0-C18.9 | Malignant neoplasm of colon |
| C19 | Malignant neoplasm of rectosigmoid junction |
| C20 | Malignant neoplasm of rectum |
| C21.0-C21.8 | Malignant neoplasm of anus and anal canal |
| C78.5 | Secondary malignant neoplasm of large intestine and rectum |
| Z85.038 | Personal history of other malignant neoplasm of large intestine |
| Z85.048 | Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus |

Document History

Revised: 02/21/2020

Document History:

- 02/21/2020– Annual Review: Remove small bowel cancer from criteria as no longer recommended by NCCN; add biosimilar reference. Coding Reviewed: Removed ICD-10-CM C17.0-C17.9, C78.4
- 05/17/2019– Annual Review: First review of Zaltrap clinical criteria. Minor wording and formatting updates. Add reference for off label criteria. Coding Reviewed: No coding changes.

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5. Van Cutsem 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(28):3499-3506.
6. Tabernero J, Van Cutsem E, Lakomy R, et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. *Eur J Cancer*. 2014; 50(2):320-331.
7. NCCN Clinical Practice Guidelines in Oncology™. © 2019 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: <http://www.nccn.org/index.asp>. Accessed on April 25, 2019.
 - a. Colon Cancer. V1.2020. Revised December 19, 2019.
 - b. Rectal Cancer. V1.2020. Revised December 19, 2019.
 - c. Anal Carcinoma. V1.2020. Revised November 19, 2019.

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