

Medical Drug Clinical Criteria

Subject: Zaltrap (ziv-aflibercept)

Document #: CC-0109

Publish Date: 04/01/2025

Status: Revised

Last Review Date: 02/21/2025

Table of Contents

[Overview](#)

[Coding](#)

[References](#)

[Clinical criteria](#)

[Document history](#)

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.

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 advanced or metastatic colon, rectal, colorectal, appendiceal, or anal adenocarcinoma (Label, NCCN 2A); **AND**
- I. The individual is unresectable, 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. Ziv-aflibercept is given in combination with cetuximab, panitumumab, or bevacizumab (or bevacizumab biosimilar); **OR**
- II. Ziv-aflibercept is used in combination with the same irinotecan-based regimen that was previously used in combination with bevacizumab (or bevacizumab biosimilar); **OR**
- III. When the above criteria are not met and for all other indications.

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

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: 02/21/2025

Document History:

- 02/21/2025 – Annual Review: add unresectable disease. Coding Reviewed: Removed ICD-10-CM Z85.068 and C78.5.
- 02/23/2024 – Annual Review: Include advanced disease per NCCN; wording and formatting updates. Coding Reviewed: No changes.
- 02/24/2023 – Annual Review: No changes. Coding Review: No changes. 02/25/2022 – Annual Review: Wording and formatting changes. Coding Reviewed: No changes.
- 02/19/2021 – Annual Review: No changes. Coding Review: No changes.

- 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.

References

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. <http://dailymed.nlm.nih.gov/dailymed/about.cfm>. Updated periodically.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2025; Updated periodically.
4. 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.
5. 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.
6. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: <http://www.nccn.org/index.asp>. Accessed on December 31, 2024.
 - a. Colon Cancer. V5.2024. Revised August 22, 2024.
 - b. Rectal Cancer. V4.2024. Revised August 22, 2024.

Federal and state laws or requirements, contract language, and Plan utilization management programs or policies may take precedence over the application of this clinical criteria.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association