



**POLICY:** Oncology – Zaltrap® (ziv-aflibercept injection for intravenous infusion – Regeneron Pharmaceutical, Inc./Sanofi-Aventis)

**APPROVAL DATE:** 09/25/2019

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## OVERVIEW

Zaltrap is a recombinant fusion protein consisting of vascular endothelial growth factor (VEGF) receptors 1 and 2 fused to the Fc portion of the human immunoglobulin G1 (IgG1).<sup>1</sup> Zaltrap acts as a soluble receptor that binds to human VEGF-A, VEGF-B, and placental growth factor (PlGF). By binding to these endogenous ligands, Zaltrap can inhibit the binding and activation of their cognate receptors, resulting in decreased neovascularization and decreased vascular permeability.

Zaltrap, in combination with FOLFIRI (5-fluorouracil [5-FU], leucovorin, and irinotecan), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.<sup>1</sup>

## GUIDELINES:

The National Comprehensive Cancer Network (NCCN) colon cancer guidelines (version 2.2019 – May 15, 2019)<sup>2</sup> and rectal cancer guidelines (version 2.2019 – May 15, 2019)<sup>3</sup> recommend Zaltrap as 1) primary treatment for patients with unresectable metachronous metastases and previous adjuvant FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) regimens within the past 12 months in combination with irinotecan OR with FOLFIRI, or 2) subsequent therapy after first progression of unresectable advanced or metastatic disease in combination with irinotecan or with FOLFIRI for disease not previously treated with an irinotecan-based regimen.<sup>2-4</sup> Both of these uses have a category 2A recommendation. In patients with advanced or metastatic disease, Zaltrap is not listed as an option for initial therapy. Zaltrap should not be used as adjuvant therapy for patients with Stage III or IV colon cancer outside of a clinical trial.

Zaltrap has only been effective when given with FOLFIRI in FOLFIRI naïve patients.<sup>2-3</sup> There are no data suggesting activity of Zaltrap plus FOLFIRI in patients who progressed on FOLFIRI plus Avastin or vice versa. No data suggest that single-agent Zaltrap has therapeutic activity. The NCCN panel includes Zaltrap as a second-line option in combination with FOLFIRI or irinotecan only after progression on therapy that does not include irinotecan. The NCCN panels on colon and rectal cancers prefer Avastin over Zaltrap and Cyramza® (ramucirumab injection for intravenous use) as an anti-angiogenic agent based on toxicity and cost.

## POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Zaltrap. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Zaltrap, as well as the monitoring required for adverse events and long-term efficacy, approval requires Zaltrap to be prescribed by or in consultation with a physician who specializes in the condition being treated.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zaltrap is recommended in those who meet the following criteria:

### FDA-Approved Indication

**1. Colon and Rectal Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

- A) Zaltrap is prescribed by or in consultation with an oncologist; AND
- B) The patient has advanced or metastatic disease; AND
- C) Patient has been previously treated with an oxaliplatin- or fluoropyrimidine-containing regimen. (Note: Fluoropyrimidines include 5-fluorouracil [5-FU], capecitabine); AND
- D) The patient has not previously been treated with FOLFIRI. (Note: Includes 5-fluorouracil [5-FU], leucovorin, and irinotecan); AND
- E) Zaltrap will be used in combination with 5-fluorouracil (5-FU) or capecitabine and/or irinotecan.

**Dosing.** Approve the following dosing regimen (A and B):

- A) Each individual dose must not exceed 4 mg/kg administered by intravenous infusion;<sup>1-3</sup> AND
- B) The dose is administered no more frequently than once every 2 weeks.<sup>1</sup>

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### CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zaltrap has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

- 1. Coverage is not recommended for circumstances not listed in the Authorization Criteria (FDA-approved indications and Other Uses with Supportive Evidence). Criteria will be updated as new published data are available.

### REFERENCES

- 1. Zaltrap® injection for intravenous infusion [prescribing information]. Bridgewater, NJ: Regeneron Pharmaceutical, Inc./sanofi-aventis U.S. LLC; June 2016.
- 2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – May 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on September 4, 2019.
- 3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – May 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on September 4, 2019.
- 4. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on September 4, 2019. Search term: ziv-aflibercept.

### HISTORY

Type of Revision	Summary of Changes*	Approval Date
Annual	No criteria changes	08/17/2016
Annual	No criteria changes	08/23/2017
Annual	No criteria changes	08/15/2018
Early annual revision	Removed preferred drug step, increased approval duration to 1 year.	02/20/2019
Early annual	No change to the criteria	09/25/2019