BlueCross BlueShield
Federal Employee Program
Blue Cross Blue Shield Association
750 9th St NW, Suite 900
Washington, D.C. 20001
1-800-624-5060
Fax 1-877-378-4727

5.21.025

Section:	Prescription Drugs	**Effective Date:**	January 1, 2025
Subsection:	Antineoplastic Agents	**Original Policy Date:**	November 1, 2012
Subject:	Zaltrap	**Page:**	1 of 5

Last Review Date: December 13, 2024

Zaltrap

Description

Zaltrap (ziv-aflibercept)

Background
Zaltrap (ziv-aflibercept) is a recombinant fusion protein consisting of Vascular Endothelial Growth Factor (VEGF)-binding portions from the extracellular domains of human VEGF receptor 1 and 2 fused to the Fc portion of the human IgG1. VEGF is responsible for creating new blood vessels to assure adequate perfusion of blood or oxygen. Inhibition of VEGF is one of the methods used in cancer treatment by cutting blood supply to cancer cells. Zaltrap works by binding to human VEGF-A to VEGF-B, and to human PIGF. By binding to these endogenous ligands, it inhibits the blood supply to tumors (1).

Regulatory Status
FDA-approved indication: Zaltrap, in combination with 5-fluorouracil, leucovorin, irinotecan–(FOLFIRI), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen (1).

Zaltrap carries a warning for hemorrhage, gastrointestinal perforation, and compromised wound healing. Severe and sometimes fatal hemorrhage, including gastrointestinal hemorrhage has been reported in patients who have received Zaltrap in combination with Folfiri. Patients must be monitored for signs and symptoms of bleeding. Do not initiate Zaltrap in patients with severe hemorrhage and discontinue in patients who develop severe hemorrhage during treatment. Gastrointestinal (GI) perforation including fatal GI perforation can occur in patients receiving Zaltrap. Patients must be monitored for signs and symptoms and discontinuation of therapy is required if patients experience gastrointestinal perforation (1).

Severe proteinuria, nephrotic syndrome, and thrombotic microangiopathy (TMA) occurred more frequently in patients treated with Zaltrap. Zaltrap administration should be suspended for proteinuria 2 grams per 24 hours or more and resumed when proteinuria is less than 2 grams per 24 hours. Discontinue Zaltrap in patients who develop nephrotic syndrome or TMA (1).

Zaltrap impairs wound healing and severe compromised wound healing can occur in patients receiving Zaltrap and therapy must be discontinued. Zaltrap therapy must be suspended for at least 4 weeks prior to elective surgery, and not to be resumed for at least 4 weeks following major surgery and until the surgical would is fully healed. For minor surgery such as central venous access port placement, biopsy, and tooth extraction, Zaltrap may be initiated/resumed once the surgical wound is fully healed (1).

The safety and effectiveness of Zaltrap have not been established in pediatric patients (1). There are no adequate and well-controlled studies with Zaltrap in pregnant women (1).

Related policies
Bevacizumab, Cyramza

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Zaltrap may be considered **medically necessary** if the conditions indicated below are met.

Zaltrap may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

Metastatic colorectal cancer (mCRC)

AND ALL of the following:

1. Concurrent use with 5-fluorouracil, leucovorin, and irinotecan

2. History of resistance to or has progressed following an oxaliplatin-containing regimen.
3. **NO** signs or symptoms of severe hemorrhage
4. **NO** signs or symptoms of gastrointestinal perforation
5. **NO** major surgery within the last 4 weeks and any wounds are fully healed

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

Metastatic colorectal cancer (mCRC)

AND ALL of the following:

1. Concurrent use with 5-fluorouracil, leucovorin, and irinotecan
2. **NO** signs or symptoms of severe hemorrhage
3. **NO** signs or symptoms of gastrointestinal perforation or fistula formation
4. Any wounds from major or minor surgery are fully healed

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Zaltrap is a recombinant Vascular Endothelial Growth Factor inhibitor approved for treatment of colorectal cancer that has spread to other parts of the body (metastatic) and that is resistant to

or has progressed after an oxaliplatin containing chemotherapy regimen. Zaltrap (ziv-aflibercept), combined with 5-fluorouracil, leucovorin, and irinotecan is approved for treatment of metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Zaltrap while maintaining optimal therapeutic outcomes.

References

1. Zaltrap [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; December 2023.
2. NCCN Drugs & Biologics Compendium ® Ziv-aflibercept 2024. National Comprehensive Cancer Network, Inc. Accessed on October 8, 2024.

Policy History

Date	Action
October 2012	New policy
December 2012	Annual editorial review and update
March 2014	Annual editorial review and reference update Addition of NO fistula formation in criteria
September 2014	Annual editorial review and reference update
March 2015	Annual editorial review and reference update
March 2016	Annual editorial review Policy number change from 5.04.25
June 2017	Annual editorial review and reference update Addition of age limits to renewal criteria
June 2018	Annual editorial review
June 2019	Annual review
December 2019	Annual review
June 2020	Annual review and reference update
December 2021	Annual review and reference update
September 2022	Annual review and reference update
June 2023	Annual review and reference update
December 2024	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 13, 2024 and is effective on January 1, 2025.