Utilization Review Policy 190

POLICY: Oncology (Injectable – Vascular Endothelial Growth Factor Inhibitors) – Zaltrap Utilization Management Medical Policy

- Zaltrap® (ziv-aflibercept intravenous infusion – Regeneron/Sanofi-Aventis)

EFFECTIVE DATE: 1/1/2020
LAST REVISION DATE: 10/15/2025

COVERAGE CRITERIA FOR: All UCare Plans

OVERVIEW

Zaltrap, a vascular endothelial growth factor inhibitor, is indicated in combination with FOLFIRI (5-fluorouracil [5-FU], leucovorin, and irinotecan), for **metastatic colorectal cancer** in patients with disease that is resistant to or has progressed following an oxaliplatin-containing regimen.[1]

Guidelines

The National Comprehensive Cancer Network **colon cancer** guidelines (version 4.2025 – June 27, 2025) and **rectal cancer** guidelines (version 3.2025 – August 26, 2025) recommend Zaltrap as:[2-4]

- Initial treatment for patients with unresectable metachronous metastases and previous 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
- Subsequent therapy after first progression of advanced or metastatic disease (proficient mismatch repair/microsatellite-stable or ineligible for or progressed on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation positive with ultra-hypermutated phenotype disease) in combination with irinotecan or with FOLFIRI for disease not previously treated with an irinotecan-based regimen.

Both of these uses have a category 2A recommendation. Zaltrap has a category 2B recommendation for use as adjuvant therapy, in combination with FOLFIRI or irinotecan, for unresectable metachronous metastases (proficient mismatch repair/microsatellite-stable or ineligible for or progressed on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation positive with ultra-hypermutated phenotype disease) that convert to resectable disease after primary treatment.

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. 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

1. **Colon and Rectal Cancer, Appendiceal Adenocarcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - i. Patient meets ALL of the following (a, b, and c):
       - a. Patient has unresectable metachronous metastases; AND
       - b. Disease is proficient mismatch repair/microsatellite-stable (pMMR/MSS) or deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation positive with ultra-hypermutated phenotype; AND
       - c. Patient meets ONE of the following [(1) or (2)]:
         - i. Patient has been previously treated with FOLFOX or CapeOX; OR
           Note: FOLFOX includes 5-fluorouracil (5-FU), leucovorin, and oxaliplatin and CapeOX includes capecitabine and oxaliplatin.
         - ii. The medication is used as adjuvant therapy.
     - ii. Patient meets ALL of the following (a, b, c, and d):
       - a. Patient has advanced or metastatic disease; AND
       - b. Disease is proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progressed on checkpoint inhibitor therapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation positive with ultra-hypermutated phenotype; AND
         Note: Examples of checkpoint inhibitors include Keytruda (pembrolizumab intravenous infusion) and Opdivo (nivolumab intravenous infusion). Ultra-hypermutated phenotype is TMB > 50 mut/MB).
       - c. The medication is used as subsequent therapy; AND
       - d. Patient has not previously been treated with irinotecan; AND
   - **C)** The medication will be used in combination with one of the following (i or ii):
     - i. Irinotecan; OR
     - ii. FOLFIRI; AND
       Note: FOLFIRI includes irinotecan, leucovorin], and 5-fluorouracil (5-FU).
   - **D)** The medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve up to 4 mg/kg administered by intravenous infusion no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zaltrap is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Zaltrap® intravenous infusion [prescribing information]. Bridgewater, NJ: Regeneron/Sanofi-Aventis; May 2025
2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 4.2025 – June 27, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 30, 2025.
3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 3.2025 – August 26, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 30, 2025.
4. The NCCN Drugs and Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 30, 2025. Search term: ziv-aflibercept.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/19/2022
Annual Revision	**Colon and Rectal Cancer, Appendiceal Adenocarcinoma:** Appendiceal Adenocarcinoma was added to the condition of approval.	10/11/2023
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024
Annual Revision	**Colon and Rectal Cancer, Appendiceal Adenocarcinoma:** Added option for approval for patient with unresectable metachronous metastases, disease is proficient mismatch repair/microsatellite-stable (pMMR/MSS), patient has been previously treated with oxaliplatin- or fluoropyrimidine-containing regimen, and the medication is used for initial therapy. Added condition of approval for patient with advanced or metastatic disease; disease that is pMMR/MSS or patient is ineligible for or progressed on checkpoint inhibitor therapy for deficient mismatch repair/microsatellite instability-high or polymerase epsilon/delta mutation positive, patient has not been previously treated with irinotecan or FOLFIRI, and medication is used for subsequent therapy. Removed descriptor "or capecitabine" from requirement that Zaltrap be used in combination with 5-fluorouracil (5-FU) and/or irinotecan.	10/16/2024
Selected Revision	**Colon and Rectal Cancer, Appendiceal Adenocarcinoma:** Revised criterion that the patient has been previously treated with an oxaliplatin- or fluoropyrimidine-containing regimen to patient has been previously treated with FOLFOX or CapeOX. Note was revised to include components of FOLFOX and CapeOX.	10/30/2024
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/15/2025
Annual Revision	The name of the policy was changed to Oncology (Injectable – Vascular Endothelial Growth Factor Inhibitors) – Zaltrap Utilization Management Medical Policy. Previously, it was "Oncology (Injectable) – Zaltrap Utilization Management Medical Policy. **Colon, Rectal, or Appendiceal Cancer:** Options for approval were added for patient with deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation positive with ultra-hypermutated phenotype. The requirement that the medication is used for initial therapy was removed. The medication is used as adjuvant therapy was added as another option for approval. Patient has not been treated with FOLFIRI was removed. The requirement that the medication will be used in combination with 5-fluorouracil was removed. The medication will be used in combination with FOLFIRI was added as another option for approval.	10/15/2025