RxAdvance

Clinical Policy Title:	ziv-aflibercept
Policy Number:	RxA.327
Drug(s) Applied:	Zaltrap®
Original Policy Date:	02/07/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Ziv-aflibercept (Zaltrap®) is a vascular endothelial growth factor (VEGF) inhibitor. 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
ziv-aflibercept (Zaltrap®)	mCRC	4 mg/kg intravenously over 1 hour every two weeks	4 mg/kg

Dosage Forms

- Single-use vial for injection: 100 mg/4 mL, 200 mg/8 mL

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Colorectal Cancer (must meet all):

1. Diagnosis of mCRC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Previous treatment with an oxaliplatin-containing regimen (e.g., FOLFOX, CapeOX);
5. Prescribed in combination with irinotecan or FOLFIRI;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 4 mg/kg every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence).*

   *Prescribed regimen must be FDA-approved or recommended by NCCN

Approval Duration:
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Colorectal Cancer (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b) *:
   a. New dose does not exceed 4 mg/kg every 2 weeks;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   *Prescribed regimen must be FDA-approved or recommended by NCCN

Approval Duration:
Commercial: 6 months
Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
CapeOX: capecitabine and oxaliplatin
mCRC: metastatic colorectal cancer
FDA: Food and Drug Administration
FOLFIRI: fluorouracil, leucovorin, irinotecan
FOLFOX: fluorouracil, leucovorin, oxaliplatin
VEGF: vascular endothelial growth factor

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
Modified FOLFOX 6	Day 1: oxaliplatin 85 mg/m2 intravenously. Give before 5-FU Day 1: Folinic acid 400 mg/m^2 intravenously over 2 hours with oxiplatin. Give before 5-FU Days 1–3: 5-FU 400 mg/m^2 intravenous bolus on day 1, then 1,200 mg/m^2/day × 2 days (total 2,400 mg/m^2 over 46–48 hours) intravenous continuous infusion. Repeat cycle every 2 weeks.	See dosing regimen
CapeOX	Day 1: Oxaliplatin 130 mg/m^2 intravenously Days 1–14: Capecitabine 850 mg/m^2 orally twice daily. Repeat cycle every 3 weeks.	See dosing regimen

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
FOLFIRI	Day 1: Irinotecan 180 mg/m^2 intravenously Day 1: Leucovorin 400 mg/m^2 intravenously Day 1: Flurouracil 400 mg/m^2 intravenously followed by 2400 mg/m^2 continuous IV over 46-48 hours. Repeat cycle every 14 days.	See dosing regimen
5-fluorouracil and leucovorin	Roswell Park regimen: Leucovorin 500 mg/m^2 IV followed by 5-FU 500 mg/m^2 intravenous bolus one hour after start of leucovorin on days 1, 8, 15, 22, 29, 36. Repeat every 8 weeks. Biweekly regimen: Leucovorin 400 mg/m^2 intravenously on day one followed by Flurouracil 400 mg/m^2 intravenously on day 1, followed by 2400 mg/m^2 continuous intravenously over 46-48 hours. Repeat cycle every 14 days. Weekly regimen: Leucovorin 20 mg/m^2 intravenously on day one followed 5-FU 500 mg/m^2 intravenously bolus one hour after start of leucovorin. Alternatively 5-FU 2,600 mg/m^2 continuous IV over 24 hours with leucovorin 500 mg/m^2 intravenously. Repeat weekly.	See dosing regimen
capecitabine	850 – 1,250 mg/m^2 PO BID on days 1-14. Repeat every 3 weeks.	2,500 mg/m^2/day

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None reported.

- Boxed Warning(s):

- None reported.

APPENDIX D: General Information

- **Hemorrhage:** Severe and sometimes fatal hemorrhage, including gastrointestinal (GI) hemorrhage, has been reported in patients who have received Zaltrap®. Do not administer Zaltrap® to patients with severe hemorrhage.
- **Gastrointestinal Perforation:** Discontinue Zaltrap® therapy in patients who experience GI perforation.
- **Impaired Wound Healing:** Withhold Zaltrap® for at least 4 weeks prior to elective surgery. Do not administer for at least 4 weeks following major surgery and until wounds have adequately healed. Discontinue Zaltrap® in patients with impaired wound healing. The safety of resumption of ZALTRAP after resolution of wound healing complications has not been established.
- **Fistula Formation:** Discontinue Zaltrap® if fistula occurs.
- **Hypertension:** Monitor blood pressure and treat hypertension. Temporarily suspend ZALTRAP if hypertension is not controlled. Discontinue Zaltrap® if hypertensive crisis develops.
- **Arterial Thromboembolic Events (ATE):** Discontinue Zaltrap® if ATE develops.
- **Proteinuria:** Monitor urine protein. Suspend ZALTRAP for proteinuria of 2 grams per 24 hours or more. Discontinue Zaltrap® if nephrotic syndrome or thrombotic microangiopathy (TMA) develops.
- **Neutropenia and Neutropenic Complications:** Delay administration of Zaltrap®/Folfiri until neutrophil count is 1.5 × 109 /L or higher.
- **Diarrhea and Dehydration:** Incidence of severe diarrhea and dehydration is increased. Monitor elderly patients more closely.
- **Reversible Posterior Leukoencephalopathy Syndrome:** Discontinue Zaltrap®.
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of potential risk to fetus and need for use of effective contraception.

References

1. Zaltrap® Prescribing Information. Bridgewater, NJ: Sanofi-Aventis U.S., LLC; December 2020. Available at http://www.zaltrap.com/. Accessed June 4, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed June 4, 2021.
3. National Comprehensive Cancer Network. Colon Cancer Version 2.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed June 4, 2021.
4. National Comprehensive Cancer Network. Rectal Cancer Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed June 4, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Clinical Policy Title was updated 2. Drug(s) Applied was updated 3. Line of Business Policy Applies to was updated 4. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by	06/24/2020	09/14/2020

RxAdvance..." 5. Commercial approval duration, Medicaid approval duration and HIM approval duration updated. 6. References were updated 7. Updated APPENDIX B: Therapeutic Alternatives for Modified FOLFOX 6 dosing regimen Day 1: oxaliplatin added 100 mg/m2 IV 8. Updated Initial Approval Criteria and Appendix A from CRC to mCRC		
Policy was reviewed: 1. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 2. Initial Approval Criteria I.A.4 was updated from “Previous treatment with one of the following (a, b, or c)…” to “Previous treatment with an oxaliplatin-containing regimen (e.g., FOLFOX, CapeOX)”. 3. Initial Approval Criteria I.A.4.a-c were updated to remove sub-criteria, “An oxaliplatin-containing regimen (e.g., FOLFOX, CapeOX)”, “A 5-fluorouracil and leucovorin-containing regimen (off-label)”, and “A capecitabine-containing regimen (off-label)” respectively. 4. Initial Approval Criteria and Continued Therapy Approval Criteria were updated to remove HIM approval duration. 5. Continued Therapy Approval Criteria II.A.1 was rephrased	5/28/2021	09/14/2021

to "Member is currently receiving medication that has been authorized by RxAdvance...". 6. Continued Therapy Approval approval duration for Medicaid was updated from “12 months” to “6 months”. 7. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 8. Appendix B: Therapeutic Alternatives dosing regimen for drug Modified FOLFOX6 was updated from “Day 1: oxaliplatin 100 mg/m2 IV” to “Day 1: oxaliplatin 85 mg/m2 intravenously”. 9. Appendix B: Therapeutic Alternatives dosing regimen for drug Modified FOLFOX6 was updated to include “…Give before 5-FU” and “…over 2 hours with oxiplatin. Give before 5-FU…”. 10. Appendix B: Therapeutic Alternatives dosing regimen for drug CapeOX was updated from “Days 1–14: Capecitabine 1,000 mg/m^2 PO BID” to “Days 1–14: Capecitabine 850 mg/m^2 orally twice daily”. 11. Appendix B: Therapeutic Alternatives dosing regimen for drug FOLFIRI was updated from “Day 1: Flurouracil 400 mg/m^2 IV followed by 2400 mg/m^2 continuous IV over 46 hours” To “Day 1: Flurouracil 400 mg/m^2 IV followed by		

2400 mg/m^2 continuous IV over 46-48 hours”. 12. Appendix B: Therapeutic Alternatives dosing regimen for drug 5-fluorouracil and leucovorin was updated from “Biweekly regimen: Leucovorin 400 mg/m2 IV on day one followed by 5-FU 400 mg/m2 IV bolus then 1,200 mg/m2 continuous IV. Repeat every 2 weeks” to “Biweekly regimen: Leucovorin 400 mg/m^2 intravenously on day one followed by Flurouracil 400 mg/m^2 intravenously on day 1, followed by 2400 mg/m^2 continuous intravenously over 46-48 hours. Repeat cycle every 14 days”. 13. Appendix B: Therapeutic Alternatives dosing regimen for drug 5-fluorouracil and leucovorin weekly regimen was updated to include “…over 24 hours…”. 14. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 15. Appendix C boxed warning was updated to remove “Hemorrhage, gastrointestinal perforation, compromised wound healing”.		

16. Appendix D was updated to include warnings and precautions, “Hemorrhage: Severe and sometimes fatal hemorrhage…”, “Gastrointestinal Perforation: Discontinue Zaltrap® therapy…”, “Impaired Wound Healing: Withhold Zaltrap® for at least 4 weeks prior…”, “Fistula Formation: Discontinue Zaltrap® if fistula occurs”, “Hypertension: Monitor blood pressure and treat hypertension…”, “Arterial Thromboembolic Events (ATE): Discontinue Zaltrap® if ATE develops”, “Proteinuria: Monitor urine protein. Suspend ZALTRAP for proteinuria…”, “Neutropenia and Neutropenic Complications: Delay administration of Zaltrap®/Folfiri…”, “Diarrhea and Dehydration: Incidence of severe diarrhea and dehydration…”, “Reversible Posterior Leukoencephalopathy Syndrome: Discontinue Zaltrap®”, and “Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of potential risk…”. 17. References were reviewed and updated.		