

Ziv-aflibercept (Zaltrap) Prior Authorization-National (PA-N) Criteria for Use August 2014

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vaww.pbm.va.gov> for further information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive ziv-aflibercept*

- Planned use of ziv-aflibercept with cetuximab, panitumumab, or bevacizumab
- Major surgery within prior 28 days (see Issues for Consideration)
- Non-healing wound or fracture (see Issues for Consideration)
- DVT, thromboembolic event within 4 weeks
- Pre-existing proteinuria (> 500 mg urine protein / 24 hours)
- Uncontrolled hypertension
- For patients of childbearing potential: Inability of both males and females to use effective contraception methods while receiving treatment with ziv-aflibercept and for at least 3 months following the last dose.

Inclusion Criteria *The answers to the following must be fulfilled in order to meet criteria.*

- Patient cancer care is being managed by a VA Oncologist
- Diagnosis of colorectal adenocarcinoma with metastatic disease not amenable to potentially curative treatment (i.e. liver metastases only)
- Progressive disease on an oxaliplatin-containing regimen
- Intended use of ziv-aflibercept in combination with FOLFIRI (5-FU, leucovorin, irinotecan)
- If patient received bevacizumab in the first-line setting under either of the following conditions, ziv-aflibercept can be considered:
 - Less than 3 months of bevacizumab in the first-line setting was given due to progressive disease OR
 - Progressive disease was evident within 3 months after first-line treatment with chemotherapy plus bevacizumab
- ECOG Performance Status 0 - 1 (see Issues for Consideration)
- No prior irinotecan given (e.g. patient should be FOLFIRI or irinotecan naïve)
- Adequate hematologic function defined as:
 - ANC \geq 1500/mm³ AND
 - Platelets \geq 100,000/mm³

Dosage and Administration

Refer to Product Information

Monitoring

- Monitor patients for signs and symptoms of bleeding; discontinue ziv-aflibercept if severe hemorrhage develops and do not initial therapy with severe bleeding.
- Monitor for signs and symptoms of GI perforation. Discontinue ziv-aflibercept in any patients who experience a GI perforation.
- Blood pressure should be monitored prior to each treatment, especially among those with age \geq 65 years. Antihypertensive therapy may be needed. Those who develop hypertension or worsening of existing HTN may require more frequent monitoring. Ziv-aflibercept should be discontinued in patients with hypertensive crises or hypertensive encephalopathy.
- Monitor for signs and symptoms of arterial thrombotic events (i.e. TIA, CVA, angina pectoris). Discontinue ziv-aflibercept therapy in patients who develop any events.
- Check urinalysis or urine dipstick and urine protein creatinine ratio (UPCR) prior to each treatment. If UPCR > 1, then obtain a 24-hour urine collection. If urine protein \geq 2 g/24 hrs, interrupt therapy until proteinuria < 2 g/24 hrs. If proteinuria is recurrent, hold therapy and resume at a permanently reduced dose of 2 mg/kg when proteinuria < 2 gm/24 hours. If nephrotic syndrome or TMA develops,

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discontinue ziv-aflibercept.

- Monitor for diarrhea, especially in the elderly patients (age \geq 65 years).
- Monitor CBC, differential at baseline and prior to each cycle. Hold ziv-aflibercept/FOLFIRI until neutrophil count \geq 1.5×10^9 L.
- Monitor recent surgical sites for evidence of compromised wound healing.
- Monitor for signs and symptoms of fistula development. Discontinue ziv-aflibercept therapy if a fistula is suspected.

Issues for Consideration

- FDA-approved indication is in combination with FOLFIRI (5-fluorouracil, leucovorin, irinotecan) for patients with metastatic colorectal cancer that is resistant to or progressed following an oxaliplatin-containing regimen
- Compromised wound healing can occur. Hold ziv-aflibercept therapy for at least 4 weeks prior to elective surgery; do not resume for at least 4 weeks following major surgery, until the surgical wound is completely healed
- Patients with ECOG PS 0-2 were included in the phase III clinical trial that led to FDA-approval. Stratification by ECOG PS indicates that the benefit of ziv-aflibercept can be achieved regardless of PS, although the confidence intervals for ECOG PS 1 and 2 crossed the value of 1 with regard to median OS. In only those patients with PS 2 did the CI cross the value of 1 with regard to PFS. Those with PS 0 appeared to consistently benefit from ziv-aflibercept. Therefore, since participants \geq 65 years experienced a higher rate of toxicity in VELOUR than their younger counterparts, these patients should be ECOG PS 0.
- Use of prior bevacizumab therapy was not an exclusion to trial participation. A prespecified subgroup analysis evaluated patients according to prior systemic bevacizumab use. Benefit from use of ziv-aflibercept was noted whether or not patients received prior bevacizumab therapy.

Renewal Criteria

- Tumor response (should be assessed every 3 cycles (every 6 weeks for MCC); if progressive disease is noted, then therapy should be discontinued
- Toxicity should be assessed prior to each cycle. Ziv-aflibercept should be discontinued in the following conditions:
 - Severe hemorrhage
 - Gastrointestinal perforation
 - Compromised wound healing
 - Fistula formation
 - Hypertensive crisis or hypertensive encephalopathy
 - Arterial thromboembolic events
 - Nephrotic syndrome or thrombotic microangiopathy (TMA)
 - Reversible posterior leukoencephalopathy syndrome (RPLS)

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