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Wolters Kluwer

Aflibercept (ziv-aflibercept) (systemic): Drug information

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(For additional information see "Aflibercept (ziv-aflibercept) (systemic): Patient drug information ")

For abbreviations and symbols that may be used in Lexicomp (show table)

ALERT: US Boxed Warning

Hemorrhage:

Severe and sometimes fatal hemorrhage, including GI hemorrhage, has been reported in patients who have received ziv-aflibercept in combination with irinotecan, leucovorin, and 5-fluorouracil (FOLFIRI). Monitor patients for signs and symptoms of GI bleeding and other severe bleeding. Do not administer ziv-aflibercept to patients with severe hemorrhage.

GI perforation:

GI perforation, including fatal GI perforation, can occur in patients receiving ziv-aflibercept. Discontinue ziv-aflibercept therapy in patients who experience GI perforation.

Compromised wound healing:

Severe compromised wound healing can occur in patients receiving ziv-aflibercept with irinotecan, leucovorin, and 5-fluorouracil. Discontinue ziv-aflibercept in patients with compromised wound healing. Suspend ziv-aflibercept for at least 4 weeks prior to elective surgery, and do not resume ziv-aflibercept for at least 4 weeks following major surgery and until the surgical wound is fully healed.

Brand Names: US

Zaltrap

Pharmacologic Category

Antineoplastic Agent; Vascular Endothelial Growth Factor (VEGF) Inhibitor

Dosing: Adult

Colorectal cancer, metastatic: IV: 4 mg/kg every 2 weeks (in combination with fluorouracil, leucovorin, and irinotecan [FOLFIRI]), continue until disease progression or unacceptable toxicity

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

There are no dosage adjustments provided in the manufacturer's labeling; however, need for adjustment is not likely because exposure in patients with mild, moderate, and severe impairment was similar to that of patients with normal renal function.

Dosing: Hepatic Impairment

Mild (total bilirubin >1 to 1.5 times ULN) to moderate (total bilirubin >1.5 to 3 times ULN) impairment:

There are no dosage adjustments provided in the manufacturer's labeling; however, need for adjustment is not likely because exposure was similar to that of patients with normal hepatic function.

Severe impairment (total bilirubin >3 times ULN): There are no dosage adjustments provided in the manufacturer's labeling (no data available).

Dosing: Adjustment for Toxicity

Arterial thrombotic events: Discontinue treatment.

Fistula formation: Discontinue treatment.

Gastrointestinal perforation: Discontinue treatment.

Hemorrhage, severe: Discontinue treatment.

Hypertension:

Recurrent or severe hypertension: Temporarily withhold treatment until controlled and then resume with a permanent dose reduction to 2 mg/kg every 2 weeks.

Hypertensive crisis or hypertensive encephalopathy: Discontinue treatment.

Neutropenia: Temporarily withhold treatment until ANC is ≥1500/mm^3.

Renal effects:

Proteinuria (≥2 g/24 hours): Temporarily withhold treatment until proteinuria <2 g/24 hours and then resume at previous dose.

Recurrent proteinuria: Temporarily withhold treatment until proteinuria <2 g/24 hours and then resume with a permanent dose reduction to 2 mg/kg every 2 weeks.

Nephrotic syndrome or thrombotic microangiopathy: Discontinue treatment

Reversible posterior leukoencephalopathy syndrome (RPLS): Discontinue treatment.

Surgery/wound healing impairment:

Elective surgery: Temporarily withhold treatment for at least 4 weeks prior to elective surgery; do not resume until at least 4 weeks after major surgery AND until wound is fully healed; for minor surgery (eg, biopsy, central venous port placement, tooth extraction), may be resumed after wound is fully healed.

Wound healing impaired: Discontinue treatment.

Note: For toxicities related to FOLFIRI, refer to individual Fluorouracil or Irinotecan monographs.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, Intravenous [preservative free]:

Zaltrap: 100 mg/4 mL (4 mL); 200 mg/8 mL (8 mL)

Generic Equivalent Available (US) No

Administration IV: Infuse over 1 hour. Do not administer as an IV push or bolus. Administer prior to any FOLFIRI component. Do not administer other medications through the same intravenous line.

Infuse via a 0.2 micron polyethersulfone filter; do not use filters made of polyvinylidene fluoride (PVDF) or nylon. Administer with one of the following types of infusion sets: Polyvinyl chloride (PVC) containing DEHP, DEHP-free PVC containing trioctyl-trimellitate (TOTM), polypropylene, polyethylene lined PVC, or polyurethane.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) for preparation. Double gloving, a gown, and (if dosage form allows) CSTDs are required during administration (NIOSH 2016).

Use **Colorectal cancer, metastatic:** Treatment of metastatic colorectal cancer (in combination with fluorouracil, leucovorin, and irinotecan [FOLFIRI]) in patients who are resistant to or have progressed on an oxaliplatin-based regimen

Medication Safety Issues

Sound-alike/look-alike issues:

Ziv-aflibercept may be confused with aflibercept

High alert medication:

This medication is in a class the Institute for Safe Medical Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions **Note:** Reactions reported in combination therapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI).

>10%:

Cardiovascular: Hypertension (41%; grade 3: 19%; grade 4: <1%)

Central nervous system: Fatigue (48%), voice disorder (25%; grades 3/4: <1%), headache (22%)

Dermatologic: Palmar-plantar erythrodysesthesia (11%)

Endocrine & metabolic: Weight loss (32%)

Gastrointestinal: Diarrhea (69%; grades 3/4: 19%), stomatitis (50%), decreased appetite (32%), abdominal pain (27%), upper abdominal pain (11%)

Genitourinary: Proteinuria (62%, grades 3/4: 8%)

Hematologic: Leukopenia (78%; grades 3/4: 16%), neutropenia (67%; grades 3/4: 37%), thrombocytopenia (48%; grades 3/4: 3%), hemorrhage (38%; grades 3/4: 3%)

Hepatic: Increased serum AST (62%), increased serum ALT (50%)

Infection: Infection (46%, grades 3/4: 12%)

Neuromuscular & skeletal: Weakness (18%; grades 3/4: 5%)

Renal: Increased serum creatinine (23%)

Respiratory: Epistaxis (28%; grades 3/4: <1%), dyspnea (12%)

1% to 10%:

Cardiovascular: Venous thromboembolic events (9%), pulmonary embolism (5%), arterial thromboembolism (3%; grades 3/4: 2%)

Central nervous system: Reversible posterior encephalopathy syndrome (1%)

Dermatologic: Hyperpigmentation (8%)

Endocrine & metabolic: Dehydration (9%; grades 3/4: 4%)

Gastrointestinal: Hemorrhoids (6%), proctalgia (5%), rectal hemorrhage (5%; grades 3/4: <1%), rectal pain (5%)

Genitourinary: Urinary tract infection (9%), nephrotic syndrome (1%)

Hematologic: Febrile neutropenia (grades 3/4: 4%)

Immunologic: Immunogenicity (3%)

Infection: Neutropenic sepsis

Respiratory: Oropharyngeal pain (8%), rhinorrhea (6%)

Miscellaneous: Fistula formation (2%; grades 3/4: <1%)

Frequency not defined:

Central nervous system: Intracranial hemorrhage (severe)

Hematologic & oncologic: Pulmonary hemorrhage

<1%, postmarketing, and/or case reports: Osteonecrosis of the jaw, reduced ejection fracture, thrombotic thrombocytopenic purpura, wound healing impairment

Contraindications There are no contraindications listed in the manufacturer’s labeling.

Warnings/Precautions

Concerns related to adverse effects:

• Bone marrow suppression: A higher incidence of neutropenia and complications due to neutropenia (neutropenic fever and infection) occurred in patients receiving ziv-aflibercept. Leukopenia and thrombocytopenia were also observed in clinical trials. Monitor CBC with differential (baseline and prior to each cycle); delay treatment until ANC is ≥1,500/mm^3.

• Diarrhea: Severe diarrhea and dehydration have been reported. The incidence of diarrhea is increased in patients ≥65 years of age; monitor elderly patients closely for diarrhea.

• Fistula formation: The risk for gastrointestinal (GI) and non-GI fistulas is increased with ziv-aflibercept. Fistula sites have included anal, enterovesical, enterocutaneous, colovaginal, and intestinal. Discontinue in patients who develop fistula.

• Gastrointestinal perforation: **[U.S. Boxed Warning]: Severe or fatal GI perforation is a possibility; discontinue ziv-aflibercept if GI perforation occurs.** Monitor for signs/symptoms of GI perforation.

• Hemorrhage: The risk for hemorrhage is increased with ziv-aflibercept. **[U.S. Boxed Warning]: Severe and occasionally fatal hemorrhage, including GI bleeding, has been reported with ziv-aflibercept/FOLFIRI. Monitor for signs and symptoms of GI and other severe bleeding events. Do not administer to patients with severe hemorrhage.** Discontinue if severe hemorrhage develops. Hemorrhagic events have also included hematuria, postprocedural hemorrhage, intracranial hemorrhage, and pulmonary hemorrhage/hemoptysis.

• Hypertension: The risk for grades 3/4 hypertension is increased. Onset is generally within the first 2 treatment cycles. Monitor blood pressure every 2 weeks (more frequently if clinically indicated). Treat with appropriate antihypertensive therapy (may require adjustment of existing antihypertensives). Temporarily withhold treatment with uncontrolled hypertension; may reinitiate with permanent dose reduction when controlled. Discontinue for hypertensive crisis or encephalopathy. Patients with NYHA class III or IV heart failure were excluded from clinical trials.

• Proteinuria/nephrotic syndrome: Proteinuria, nephrotic syndrome, and thrombotic microangiopathy (TMA) have been associated with ziv-aflibercept. Evaluate for proteinuria during treatment with urine dipstick and/or urinary protein creatinine ratio (UPCR); if dipstick ≥2+ for protein or UPCR >1, obtain 24-hour urine collection. Withhold ziv-aflibercept for proteinuria ≥2 g per 24 hours; for recurrent proteinuria, withhold treatment until <2 g per 24 hours and then resume with permanent dose reduction. Discontinue treatment for nephrotic syndrome or TMA.

• Reversible posterior leukoencephalopathy syndrome (RPLS): Cases of RPLS have been reported. Confirm diagnosis with MRI; discontinue ziv-aflibercept if verified. Symptoms generally resolve or improve within days, although persistent neurologic symptoms and death have been reported.

• Thromboembolism: Arterial thrombotic events (ATE), including transient ischemic attack, cerebrovascular accidents, and angina have occurred. Discontinue ziv-aflibercept in patients who experience ATEs.

• Wound healing impairment: **[U.S. Boxed Warning]: Severely compromised wound healing may occur with ziv-aflibercept/FOLFIRI. Discontinue ziv-aflibercept with compromised**

wound healing. Withhold ziv-aflibercept at least 4 weeks prior to elective surgery. Do not resume ziv-aflibercept treatment until at least 4 weeks after major surgery AND until the surgical wound is completely healed. For minor surgeries (eg, central venous access port placement, biopsy, or tooth extraction), ziv-aflibercept may be resumed or initiated as soon as the surgical wound is fully healed.

Special populations:

• Elderly: Certain adverse events, such as diarrhea, dizziness, weakness, weight loss, and dehydration, occurred at a higher incidence in elderly compared to younger adults; monitor closely during treatment.

Metabolism/Transport Effects

None known.

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Bisphosphonate Derivatives: Systemic Angiogenesis Inhibitors may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Specifically, the risk for osteonecrosis of the jaw may be increased. *Risk C: Monitor therapy*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Pregnancy Risk Factor

C (show table)

Pregnancy Implications

Adverse events were observed in animal reproduction studies with doses providing systemic exposure equivalent to ~30% of a human dose. The incidence of fetal malformations increased with increasing doses. Patients (male and female) should use effective contraception during therapy and for at least 3 months following treatment.

Breast-Feeding Considerations

It is not known if ziv-aflibercept is excreted into breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends a decision to be made whether to discontinue nursing or to discontinue aflibercept, taking into account the importance of treatment to the mother.

Monitoring Parameters

CBC with differential (baseline and prior to each cycle); urine protein (dipstick analysis and/or urinary protein creatinine ratio [UPCR], obtain 24-hour urine collection if dipstick ≥2+

for protein or UPCR >1); blood pressure (every 2 weeks; more frequently if clinically indicated); monitor for signs/symptoms of hemorrhage or GI perforation; monitor elderly patients closely for diarrhea and/or dehydration. Monitor wounds for healing impairment.

Mechanism of Action Also known as VEGF-trap, ziv-aflibercept is a recombinant fusion protein which is comprised of portions of binding domains for vascular endothelial growth factor (VEGF) receptors 1 and 2, attached to the Fc portion of human IgG1. Ziv-aflibercept acts as a decoy receptor for VEGF-A, VEGF-B, and placental growth factor (PlGF) which prevent VEGF receptor binding/activation to their receptors (an action critical to angiogenesis), thus leading to antiangiogenesis and tumor regression.

Pharmacodynamics/Kinetics Half-life elimination: ~6 days (range: 4 to 7 days)

Pricing: US

Solution (Zaltrap Intravenous)

100 mg/4 mL (4 mL): $1920.00

200 mg/8 mL (8 mL): $3840.00

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names Aflitiv (AU); Lidaveg (AU); Zaltrap (AT, AU, BE, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, HK, HR, HU, IL, IS, LT, LU, LV, MT, NL, NO, PT, QA, RO, SE, SI, SK, TH, TR)

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