SANOFI REGENERON

# ZALTRAP® (ziv-aflibercept) Injection for Intravenous Infusion Overview

**What is angiogenesis?**

- In cancer, angiogenesis is the process by which new blood vessels are formed. Because tumors secrete growth factors that result in the formation of new blood vessels and enable the tumor to grow, inhibiting these angiogenic factors has become an important area of oncology research.

- The Vascular Endothelial Growth Factor (VEGF) family includes proteins that promote angiogenesis by binding to VEGF receptors on endothelial cells within existing blood vessels. One pathway to inhibit angiogenesis is to prevent circulating VEGF angiogenic growth factors from binding to their specific receptors.
    - Vascular Endothelial Growth Factor-A (VEGF-A, sometimes referred to as VEGF) is one of the mediators contributing to angiogenesis. VEGF-B and placental growth factor (PlGF), related growth factors in the VEGF family, may contribute to tumor angiogenesis as well.

**What is ZALTRAP and how does it work?**

- ZALTRAP is a recombinant fusion protein, which acts as a soluble receptor that binds to VEGF-A, VEGF-B and PlGF.
    - Inhibition of these factors can result in decreased neovascularization and decreased vascular permeability.

- ZALTRAP was approved by the U.S. Food and Drug Administration in August 2012 for use in combination with 5-fluorouracil, leucovorin, irinotecan (FOLFIRI), in patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

- ZALTRAP was discovered by Regeneron Pharmaceuticals and co-developed with Sanofi. Sanofi and Regeneron will co-commercialize ZALTRAP in the United States.

**Important Safety Information for ZALTRAP**

**WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, COMPROMISED WOUND HEALING**

**Severe and sometimes fatal hemorrhage, including gastrointestinal (GI) hemorrhage, has been reported in the patients who have received ZALTRAP in combination with FOLFIRI. Monitor patients for signs and symptoms of GI bleeding and other severe bleeding. Do not administer ZALTRAP to patients with severe hemorrhage.**

**GI perforation including fatal GI perforation can occur in patients receiving ZALTRAP. Discontinue ZALTRAP therapy in patients who experience GI perforation.**

**Severe compromised wound healing can occur in patients receiving ZALTRAP/FOLFIRI. Discontinue ZALTRAP in patients with compromised wound healing. Suspend ZALTRAP for at least 4 weeks prior to elective surgery, and do not resume ZALTRAP for at least 4 weeks following major surgery and until the surgical wound is fully healed.**

Please see additional Important Safety Information on pages 2-4 and the accompanying full Prescribing Information, including Boxed WARNING.

**What pivotal clinical trial data supported the ZALTRAP approval?**

- Approval is based on data from the pivotal Phase III VELOUR trial, a multinational, randomized, double-blind trial comparing FOLFIRI in combination with either ZALTRAP or placebo in the treatment of patients with mCRC. The study randomized 1,226 patients with mCRC who previously had been treated with an oxaliplatin-containing regimen. Twenty-eight percent of patients in the study received prior bevacizumab therapy. The primary endpoint was an improvement in overall survival. Secondary endpoints included progression-free survival, overall response rate, and safety.

- The VELOUR trial showed that in patients previously treated with an oxaliplatin containing regimen, adding ZALTRAP to FOLFIRI significantly improved median survival from 12.06 months to 13.50 months (HR=0.817 (95% CI 0.714 to 0.935; p=0.0032), an 18 percent relative risk reduction . A significant improvement in progression-free survival from 4.67 months to 6.90 months (HR=0.758 95% CI 0.661 to 0.869; p=0.00007), a 24 percent relative risk reduction, was also observed. The overall response rate in the ZALTRAP plus FOLFIRI arm was 19.8% vs. 11.1% for FOLFIRI (p=0.0001).

- The most common adverse reactions (all grades, ≥20% incidence) reported at a higher incidence (2% or greater between-arm difference) in the ZALTRAP/FOLFIRI arm, in order of decreasing frequency, were leukopenia, diarrhea, neutropenia, proteinuria, AST increased, stomatitis, fatigue, thrombocytopenia, ALT increased, hypertension, weight decreased, decreased appetite, epistaxis, abdominal pain, dysphonia, serum creatinine increased, and headache. The most common Grade 3-4 adverse reactions (≥5%) reported at a higher incidence (2% or greater between-arm difference) in the ZALTRAP/FOLFIRI arm, in order of decreasing frequency, were neutropenia, diarrhea, hypertension, leukopenia, stomatitis, fatigue, proteinuria, and asthenia.

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**Severe compromised wound healing can occur in patients receiving ZALTRAP/FOLFIRI. Discontinue ZALTRAP in patients with compromised wound healing. Suspend ZALTRAP for at least 4 weeks prior to elective surgery, and do not resume ZALTRAP for at least 4 weeks following major surgery and until the surgical wound is fully healed.**

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**Important Safety Information for ZALTRAP® (ziv-aflibercept) Injection for Intravenous Infusion (Cont.)**

**WARNINGS AND PRECAUTIONS**

- Patients treated with ZALTRAP have an increased risk of hemorrhage, including severe and sometimes fatal hemorrhagic events.
  - Monitor patients for signs and symptoms of bleeding.
  - Do not initiate ZALTRAP to patients with severe hemorrhage.
  - Discontinue ZALTRAP in patients who develop severe hemorrhage.

- GI perforation including fatal GI perforation can occur in patients receiving ZALTRAP.
  - Monitor patients for signs and symptoms of GI perforation.
  - Discontinue ZALTRAP in patients who experience GI perforation.

- Discontinue ZALTRAP in patients with compromised wound healing.
  - Suspend ZALTRAP for at least 4 weeks prior to elective surgery
  - Do not initiate/resume ZALTRAP until at least 4 weeks after surgery and surgical wound is fully healed.

- Fistula formation involving GI and non-GI sites occurs at a higher incidence in patients treated with ZALTRAP. Discontinue ZALTRAP therapy in patients who develop fistula.

- An increased risk of Grade 3-4 hypertension has been observed in patients receiving ZALTRAP.
  - Monitor blood pressure every two weeks or more frequently and treat with appropriate anti-hypertensive therapy during treatment with ZALTRAP.
  - Temporarily suspend ZALTRAP until hypertension is controlled, and reduce ZALTRAP dose to 2 mg/kg for subsequent cycles.
  - Discontinue ZALTRAP in patients with hypertensive crisis.

- Arterial thromboembolic events (ATE), including transient ischemic attack, cerebrovascular accident, and angina pectoris, occurred more frequently in patients who have received ZALTRAP. Discontinue ZALTRAP in patients who experience an ATE.

- Severe proteinuria, nephrotic syndrome, and thrombotic microangiopathy (TMA) occurred more frequently in patients treated with ZALTRAP.
  - Suspend ZALTRAP when proteinuria ≥2 grams/24 hours and resume ZALTRAP when proteinuria <2 grams/24 hours.
  - If recurrent, suspend until proteinuria <2 grams/24hours and then reduce ZALTRAP dose to 2 mg/kg.
  - Discontinue ZALTRAP if nephrotic syndrome or TMA develops.

- A higher incidence of neutropenic complications (febrile neutropenia and neutropenic infection) occurred in patients receiving ZALTRAP.
  - Delay administration of ZALTRAP/FOLFIRI until neutrophil count is ≥1.5 x $10^9$/L.

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**Important Safety Information for ZALTRAP® (ziv-aflibercept) Injection for Intravenous Infusion (Cont.)**

- Incidence of severe diarrhea and dehydration is increased in patients treated with ZALTRAP/FOLFIRI.
  - The incidence of diarrhea is increased in patients ≥65 years of age. Monitor closely.
- Discontinue ZALTRAP in patients who develop reversible posterior leukoencephalopathy syndrome.

**ADVERSE REACTIONS**

- The most common adverse reactions (all grades, ≥20% incidence) reported at a higher incidence (2% or greater between-arm difference) in the ZALTRAP/FOLFIRI arm, in order of decreasing frequency, were leukopenia, diarrhea, neutropenia, proteinuria, AST increased, stomatitis, fatigue, thrombocytopenia, ALT increased, hypertension, weight decreased, decreased appetite, epistaxis, abdominal pain, dysphonia, serum creatinine increased, and headache.
- The most common Grade 3-4 adverse reactions (≥5%) reported at a higher incidence (2% or greater between-arm difference) in the ZALTRAP/FOLFIRI arm, in order of decreasing frequency, were neutropenia, diarrhea, hypertension, leukopenia, stomatitis, fatigue, proteinuria, and asthenia.
- Infections occurred at a higher frequency in patients receiving ZALTRAP/FOLFIRI (46%, all grades; 12%, Grade 3-4) than in patients receiving placebo/FOLFIRI (33%, all grades; 7%, Grade 3-4), including urinary tract infection, nasopharyngitis, upper respiratory tract infection, pneumonia, catheter site infection, and tooth infection.
- In patients with mCRC, venous thromboembolic events (VTE), consisting primarily of deep venous thrombosis and pulmonary embolism, occurred in 9% of patients treated with ZALTRAP/FOLFIRI and 7% of patients treated with placebo/FOLFIRI.

Please see accompanying full Prescribing Information, including Boxed WARNING, and visit: www.ZALTRAP.com

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