To: Managed Care Health Care Professionals

From: Sanofi US and Regeneron Pharmaceuticals, Inc.

Subject: New FDA Approval for Metastatic Colorectal Cancer

NEW
ZALTRAP®
(ziv-aflibercept)
Injection for Intravenous Infusion

Sanofi US and Regeneron Pharmaceuticals, Inc. are pleased to announce that the U.S. Food and Drug Administration (FDA) has approved ZALTRAP® (ziv-aflibercept) Injection for Intravenous Infusion.

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. The recommended dose of ZALTRAP administered as an intravenous infusion over 1 hour, is 4 mg per kg of body weight every 2 weeks, prior to any component of the FOLFIRI regimen on the day of treatment.

ZALTRAP® will be available to administer to patients in late August. However, your Sanofi Account Manager will be contacting you shortly to provide additional information that will be useful in determining the most appropriate medical policy at your health plan for this new treatment option.

IMPORTANT SAFETY INFORMATION FOR
ZALTRAP® (ZIV-AFLIBERCEPT) INJECTION FOR INTRAVENOUS INFUSION

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.

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/24 hours 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 $\geq 1.5 \times 10^9$/L.

- 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 click here for full Prescribing Information including Boxed **WARNING**.

For more information on ZALTRAP®, please visit **www.ZALTRAP.com** or contact us at **1-855-ZALTRAP (1-855-925-8727)**.

SANOFI REGENERON