To: (insert name of individual)

From: (insert your name and title)

Subject: J-Code Update

The Centers for Medicare and Medicaid Services (CMS) have granted ZALTRAP® (Ziv-Aflibercept) Injection for Intravenous Infusion a permanent J Code. J9400. This new HCPCS code is effective for dates of service on or after January 1, 2014. Please be sure to prepare your systems for the introduction of this new code.

Attached, is the following document:

- Updated Billing and Coding Guide with new J-Code information
- ZALTRAP (ziv-aflibercept) full prescribing information, including Boxed WARNING.

Please do not hesitate to contact your Sanofi Reimbursement Representative if you have any questions.

Please see attached full Prescribing Information, including Boxed WARNING.
ZALTRAP® (ziv-aflibercept)
Injection for Intravenous Infusion
Initial U.S. Approval: 2012

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, COMPROMISED WOUND HEALING
See full prescribing information for complete boxed warning.

- 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. (5.1)
- Gastrointestinal Perforation: Discontinue ZALTRAP therapy in patients who experience GI perforation. (5.2)
- Compromised Wound Healing: Discontinue ZALTRAP in patients with compromised wound healing. Suspend ZALTRAP for at least 4 weeks prior to elective surgery, and do not resume for at least 4 weeks following major surgery and until the surgical wound is fully healed. (5.3)

RECENT MAJOR CHANGES

Warnings and Precautions (5.7) 10/2013

INDICATIONS AND USAGE

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. (1) Dose: 4 mg/kg as an intravenous infusion over 1 hour every 2 weeks. (2.1, 2.4)

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, COMPROMISED WOUND HEALING

DOSAGE AND ADMINISTRATION

4 mg/kg as an intravenous infusion over 1 hour every 2 weeks. (2.1, 2.4)
- Do not administer as an intravenous (IV) push or bolus. (2.4)

DOSE FORMS AND STRENGTHS

- Single-use vials: 100 mg/4 mL (25 mg/mL), 200 mg/8 mL (25 mg/mL) (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

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2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dose and Schedule
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4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
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13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
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14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
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17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

None (4)

WARNINGS AND PRECAUTIONS
Adverse reactions, sometimes severe and life-threatening or fatal, have been seen in clinical trials with ZALTRAP, including:
- Fistula Formation: Discontinue ZALTRAP if fistula occurs. (2.2, 5.4)
- Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend ZALTRAP if hypertension is not controlled. Discontinue ZALTRAP if hypertensive crisis develops. (2.2, 5.5)
- Arterial Thromboembolic Events (ATE) (e.g., transient ischemic attacks, cerebrovascular accident, angina pectoris): Discontinue ZALTRAP if ATE develops. (5.6)
- Proteinuria: Monitor urine protein. Suspend ZALTRAP when proteinuria ≥ 2 grams per 24 hours. Discontinue ZALTRAP if nephrotic syndrome or thrombotic microangiopathy (TMA) develops. (2.2, 5.7)
- Neutropenia and Neutropenic Complications: Delay administration of ZALTRAP/FOLFIRI until neutrophil count is ≥ 1.5 x 10^9/L. (5.8)
- Diarrhea and Dehydration: Incidence of severe diarrhea and dehydration is increased. Monitor elderly patients more closely. (5.9, 5.8)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Discontinue ZALTRAP. (5.10)

ADVERSE REACTIONS
Most common adverse reactions (all grades, ≥20% incidence and at least 2% greater incidence for the ZALTRAP/FOLFIRI regimen) were leukopenia, diarrhea, neutropenia, proteinuria, AST increased, stomatitis, fatigue, thrombocytopenia, ALT increased, hypertension, weight decreased, decreased appetite, opisthotonos, abdominal pain, dyspnea, serum creatinine increased, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS
- Pregnancy: Based on animal data, ZALTRAP may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue drug or nursing taking into account the importance of the drug to the mother. (8.3)
- Females and Males of Reproductive Potential: Use highly effective contraception during and up to a minimum of 3 months after the last dose (8.9)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2013
with 1% of patients receiving placebo/FOLFIRI. Severe intracranial hemorrhage and pulmonary hemorrhage/hemoptysis including fatal events have also occurred in patients treated with ZALTRAP. Monitor patients for signs and symptoms of bleeding. Do not initiate ZALTRAP in patients with severe hemorrhage. Discontinue ZALTRAP in patients who develop severe hemorrhage [see Dosage and Administration (2.2)].

5.2 Gastrointestinal Perforation
Gastrointestinal (GI) perforation including fatal GI perforation can occur in patients receiving ZALTRAP. Across three Phase 3 placebo-controlled clinical studies (colorectal, pancreatic, and lung cancer populations), the incidence of GI perforation (all grades) was 0.8% for patients treated with ZALTRAP and 0.2% for patients treated with placebo. Grade 3–4 GI perforation in patients treated with ZALTRAP and 0.2% of patients treated with placebo. Monitor patients for signs and symptoms of GI perforation. Discontinue ZALTRAP therapy in patients who experience GI perforation [see Dosage and Administration (2.2)].

5.3 Compromised Wound Healing
ZALTRAP impairs wound healing in animal models [see Nonclinical Toxicology (13.2)]. Grade 3 compromised wound healing was reported in 2 patients (0.3%) treated with ZALTRAP/FOLFIRI regimen and in none of the patients treated with placebo/FOLFIRI regimen. Severe compromised wound healing occurred in 1 patient treated with ZALTRAP/FOLFIRI for at least 4 weeks following major surgery and until the surgical wound is fully healed [see Dosage and Administration (2.2), Warnings and Precautions (5.3)].

5.4 Fistula Formation
Fistula formation involving gastrointestinal and non-gastrointestinal sites occurs at a higher incidence in patients treated with ZALTRAP. In patients with mCRC, fistulas (anal, enterovesical, enteroentero- cutaneous, colovaginal, intestinal sites) were reported in 9 of 611 patients (1.5%) treated with ZALTRAP/FOLFIRI regimen and 3 of 605 patients (0.5%) treated with placebo/FOLFIRI regimen. Grade 3 GI fistula formation occurred in 2 patients treated with ZALTRAP (0.3%) and in 1 placebo-treated patient (0.2%). Discontinue ZALTRAP therapy in patients who develop fistula [see Dosage and Administration (2.2)].

5.5 Hypertension
ZALTRAP increases the risk of Grade 3–4 hypertension. There is no clinical trial experience administering ZALTRAP to patients with NYHA class III or IV heart failure. In patients with mCRC, Grade 3 hypertension (defined as requiring adjustment in existing anti-hypertensive therapy or treatment with more than one drug) was reported in 1.5% of patients treated with placebo/FOLFIRI and 19% of patients treated with ZALTRAP/FOLFIRI. Grade 4 hypertension (hypertensive crisis) was reported in 1 patient (0.2%) treated with ZALTRAP/FOLFIRI. Among those patients treated with ZALTRAP/FOLFIRI during a 3–4 hypertension, 54% had onset during the first two cycles of treatment. Monitor blood pressure every two weeks or more frequently as clinically indicated during treatment with ZALTRAP. Treat with appropriate anti-hypertensive therapy and continue monitoring blood pressure regularly. Temporarily suspend ZALTRAP in patients with uncontrolled hypertension until controlled, and permanently reduce ZALTRAP dose to 2 mg per kg for subsequent cycles. Discontinue ZALTRAP in patients with hypertension or severe hypertension [see Dosage and Administration (2.2)].

5.6 Arterial Thromboembolic Events
Arterial thromboembolic events (ATE), including transient ischemic attack, cerebrovascular accident, and angina pectoris, occurred more frequently in patients who have received ZALTRAP. In patients with mCRC, ATE was reported in 2.6% of patients treated with ZALTRAP/FOLFIRI and 1.7% of patients treated with placebo/FOLFIRI. Grade 3–4 events occurred in 11 patients (1.8%) treated with ZALTRAP/FOLFIRI and 4 patients (0.7%) treated with placebo/FOLFIRI. Discontinue ZALTRAP in patients who experience an ATE [see Dosage and Administration (2.2)].

5.7 Proteinuria
Severe proteinuria, nephrotic syndrome, and thrombotic microangiopathy (TMA) occurred more frequently in patients treated with ZALTRAP compared to those treated with placebo. In patients with mCRC, proteinuria >2 grams per 24 hours was reported in 82% patients treated with ZALTRAP/FOLFIRI compared to 41% patients treated with placebo/FOLFIRI. Grade 3–4 proteinuria occurred in 8% of patients treated with ZALTRAP/FOLFIRI to 1% of patients treated with placebo/FOLFIRI [see Adverse Reactions (6.1)]. Nephrotic syndrome occurred in 2 patients (0.1%) treated with ZALTRAP/FOLFIRI compared to none of the patients treated with placebo/FOLFIRI. TMA was reported in 3 of 2258 patients with cancer enrolled across completed studies. Monitor proteinuria by urine dipstick analysis and/or urinary protein creatinine ratio (UPCR) for the development or worsening of proteinuria during ZALTRAP therapy. Patients with a dipstick of ≥2+ for protein or a UPCR greater than or equal to 3.4-hour urine collection. Suspend ZALTRAP administration for proteinuria 2 grams per 24 hours or more, and resume when proteinuria is less than 2 grams per 24 hours. If recurrent, suspend proteinuria is less than 2 grams per 24 hours and then permanently reduce the ZALTRAP dose to 2 mg per kg. Discontinue ZALTRAP in patients who develop nephrotic syndrome or TMA [see Dosage and Administration (2.2)].

5.8 Neutropenia and Neutropenic Complications
A higher incidence of neutropenic complications (febrile neutropenia and neutropenic infection) occurred in patients receiving ZALTRAP. In patients with mCRC, Grade 3–4 neutropenia was more frequent in patients treated with ZALTRAP/FOLFIRI compared to those treated with placebo/FOLFIRI [see Adverse Reactions (6.1)]. Grade 3–4 febrile neutropenia occurred in 7% of patients treated with ZALTRAP/FOLFIRI compared to 0% of patients treated with placebo/FOLFIRI. Grade 4–5 neutropenia infection/sepsis occurred in 1.5% of patients treated with ZALTRAP/FOLFIRI and 1.2% of patients treated with placebo/FOLFIRI. Monitor CBC with differential count at baseline and prior to initiation of each cycle of ZALTRAP. Delay ZALTRAP/FOLFIRI until neutrophil count is at or above 1.5 x 10^9/L.

5.9 Diarrhea and Dehydration
The incidence of severe diarrhea is increased in patients treated with ZALTRAP/FOLFIRI. In patients with mCRC, Grade 3–4 diarrhea was reported in 19% of patients treated with ZALTRAP/FOLFIRI compared to 8% of patients treated with placebo/FOLFIRI. Grade 3–4 dehydration was reported in 4% of patients treated with ZALTRAP/FOLFIRI compared to 1% of patients treated with placebo/FOLFIRI [see Adverse Reactions (6.1)]. The incidence of diarrhea is increased in patients aged 65 years or older as compared to patients younger than 65 years of age [see Geriatric Use (8.5)]. Monitor elderly patients closely for diarrhea.

5.10 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
RPLS was also known as posterior leukoencephalopathy. RPLS was reported in 0.5% of 1936 patients treated with ZALTRAP monotherapy or in combination with chemotherapy. Confirm the diagnosis of RPLS with MRI and discontinue ZALTRAP in patients who develop RPLS. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae or death [see Dosage and Administration (2.2)].
6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:
- Hemorrhage [see Boxed Warning, Warnings and Precautions (5.1)]
- Gastrointestinal Perforation [see Boxed Warning, Warnings and Precautions (5.2)]
- Compromised Wound Healing [see Boxed Warning, Warnings and Precautions (5.3)]
- Fatui Formation [see Warnings and Precautions (5.4)]
- Hypertension [see Warnings and Precautions (5.5)]
- Arterial Thromboembolic Events [see Warnings and Precautions (5.6)]
- Proteinuria [see Warnings and Precautions (5.7)]
- Neutropenia and Neutropenic Complications [see Warnings and Precautions (5.8)]
- Diarrhea and Dehydration [see Warnings and Precautions (5.9)]
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) [see Warnings and Precautions (5.10)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under varying designs and in different patient populations, the adverse reaction rates reported in one clinical trial may not be easily compared to those reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The safety of ZALTRAP in combination with FOLFIRI was evaluated in 1216 previously treated patients with metastatic colorectal cancer (Study 1) who were treated with ZALTRAP 4 mg per kg intravenous in another clinical trial, and may not reflect the rates actually observed in clinical practice. The adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

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 diarrhea, neutropenia, proteinuria, AST increased, fatigue, thrombocytopenia, ALT increased, hypertension, weight decreased, decreased appetite, epistaxis, abdominal pain, dysphonia, serum creatinine increased, and headache (see Table 1).

The most common Grade 3–4 adverse reactions (≥25% 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 (see Table 1).

The most frequent adverse reactions leading to permanent discontinuation in 21% of patients treated with ZALTRAP/FOLFIRI regimen were asthenia/fatigue, infections, diarrhea, dehydration, hypertension, stomatitis, venous thromboembolic events, neutropenia, and proteinuria.

The ZALTRAP dose was reduced and/or discontinued in 17% of patients compared to placebo-dose modification in 5% of patients. Cycle delays >7 days occurred in 60% of patients treated with ZALTRAP/FOLFIRI compared with 43% of patients treated with placebo/FOLFIRI.

The most common adverse reactions and laboratory abnormalities during study treatment in Study 1 were:

<table>
<thead>
<tr>
<th>Primary System Organ Class</th>
<th>Placebo/FOLFIRI (N=605)</th>
<th>ZALTRAP/FOLFIRI (N=611)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>72%</td>
<td>78%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>57%</td>
<td>67%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>35%</td>
<td>48%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>24%</td>
<td>32%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11%</td>
<td>41%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastial disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>7%</td>
<td>28%</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>3%</td>
<td>25%</td>
</tr>
<tr>
<td>Dyspea</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td>Oropharyngeal Pain</td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>Rhinorrea</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57%</td>
<td>69%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>33%</td>
<td>53%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>24%</td>
<td>27%</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>Rectal Hemorrhage</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Proctalgia</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-Plantar Erythrodysesthesia</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>Syndrome</td>
<td>4%</td>
<td>11%</td>
</tr>
<tr>
<td>Skin Hyperpigmentation</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>41%</td>
<td>62%</td>
</tr>
<tr>
<td>Serum creatinine increased</td>
<td>19%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Note: Adverse Reactions are reported using MedDRA version MEDDRA13.1 and graded using NCI CTCAE version 3.0.

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, severe hypersensitivity reactions have been reported with ZALTRAP/FOLFIRI (0.3%) and placebo/FOLFIRI (0.5%).

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ZALTRAP with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No dedicated clinical interaction studies have been conducted for ZALTRAP. No clinically important pharmacokinetic drug-drug interactions were found between ziv-aflibercept and intravenous 5-FU, based on cross-study comparisons and population pharmacokinetic analyses.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Pediatric Use

The safety and effectiveness in pediatric patients have not been established.

Other species

The effects of ZALTRAP on fertility were not studied in male or female rats. ZALTRAP was given to female rats for 14 days starting at the beginning of organogenesis at twice the recommended dose (2×R). No adverse effects on fertility were noted. No studies were conducted in male rats.

8.6 Hepatic Impairment

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of ziv-aflibercept.
Hepatic impairment
Male and female reproductive function and fertility may be compromised during treatment with ZALTRAP, as suggested by findings in monkeys (see Nonclinical Toxicology) [13.7]. These animal findings were not reversible within 18 weeks after cessation of treatment. Females and males of reproductive potential should use highly effective contraception during and up to a minimum of 3 months after the last dose of treatment.

10 OVERTOXISITY
There have been no cases of overdose reported with ZALTRAP. There is no information on the safety of ZALTRAP given at doses exceeding 7 mg per kg every 2 weeks or 9 mg per kg every 3 weeks.

11 DESCRIPTION
Ziv-aflibercept is a recombinant fusion protein consisting of Vascular Endothelial Growth Factor (VEGF)-binding portions from the extracellular domains of human VEGF Receptors 1 and 2 fused to the Fc portion of the human IgG1. Ziv-aflibercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) K-1 mammalian expression system. Ziv-aflibercept is a dimeric glycoprotein with a molecular weight of 97 kdaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa.

ZALTRAP is a sterile, colorless to pale yellow, non-pyrogenic, preservative-free, solution for administration by intravenous infusion. ZALTRAP is supplied in single-use vials of 100 mg per 4 mL and 200 mg per 8 mL of ziv-aflibercept in polymer-coated vials (20 ± 1%), sodium chloride (100 mM), sodium citrate (5 mM), sodium phosphate (5 mM), and sucrose (20%), in water for injection USP, at a pH of 6.2.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Ziv-aflibercept acts as a soluble receptor that binds to human VEGF-A (equilibrium dissociation constant $K_d$ of 0.5 pM for VEGF-A$_{165}$, and 0.36 pM for VEGF-A$_{121}$, to human VEGF-B ($K_d$ of 1.92 pM), and to human PIGF ($K_d$ of 39 pM for PIGF-2). By binding to these endogenous ligands, ziv-aflibercept can inhibit the binding and activation of their receptors. This inhibition can result in decreased neovascularization and decreased vascular permeability. In animals, ziv-aflibercept was shown to inhibit the proliferation of endothelial cells, thereby inhibiting the growth of new blood vessels. Ziv-aflibercept inhibited the growth of xenotransplanted colon tumors in mice.

12.2 Pharmacokinetics
Plasma concentrations of free and VEGF-bound ziv-aflibercept were measured using specific enzyme-linked immunosorbent assay (ELISAs). Free ziv-aflibercept concentrations appear to exhibit linear pharmacokinetics in the dose range of 2-9 mg/kg. Following four 2-weekly intravenous administrations of ZALTRAP, the elimination half-life of free ziv-aflibercept was approximately 6 days (range 4–7 days). Steady state concentrations of free ziv-aflibercept were reached by the second dose. The accumulation ratio for free ziv-aflibercept was approximately 1.2 after administration of 4 mg/kg every 2 weeks.

Specific Populations
Based on a population pharmacokinetic analysis, age, race, and gender did not have a clinically important effect on the exposure of free ziv-aflibercept. Patients weighing $\geq$100 kg had a 29% increase in systemic exposure compared to patients weighing 50 to 100 kg.

Hepatic impairment
Based on a population pharmacokinetic analysis which included patients with mild (total bilirubin $\leq$1.5×–3× ULN and any SGOT/AST, n=63) and moderate (total bilirubin $>3$×–5× ULN and any SGOT/AST, n=5) hepatic impairment, there was no effect of total bilirubin, aspartate amino transferase, or creatinine clearance on the clearance of free ziv-aflibercept. There is no information on the safety of ZALTRAP given at doses exceeding 7 mg per kg every 2 weeks or 9 mg per kg every 3 weeks.

12.3 Cardiac Electrophysiology
The effect of 6 mg/kg intravenous ZALTRAP every three weeks on QTc interval was evaluated in 87 patients with solid tumors in a randomized, placebo-controlled study. No large changes in the mean QTc interval from baseline (i.e., greater than 20 ms as corrected for placebo) based on Fridericia correction method were detected in the study. However, a small increase in the mean QTc interval (i.e., greater than 20 ms as corrected for placebo) was observed at the 6 mg/kg intravenous ZALTRAP (N=612).

Table 1 – Overview of efficacy results for the ZALTRAP/FOLFIRI regimen versus the placebo/FOLFIRI regimen

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>N (%)</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/FOLFIRI</td>
<td>614</td>
<td>0.0032</td>
<td>0.817 (0.714 to 0.935)</td>
</tr>
<tr>
<td>ZALTRAP/FOLFIRI</td>
<td>612</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
ZALTRAP is supplied in 5 mL and 10 mL vials containing ziv-aflibercept at a concentration of 25 mg/mL.

NDC 0024-5840-01: carton containing three (3) single-use vials of 100 mg per 4 mL (25 mg/mL)

NDC 0024-5840-03: carton containing three (3) single-use vials of 100 mg per 4 mL (25 mg/mL)

NDC 0024-5841-01: carton containing one (1) single-use vial of 200 mg per 8 mL (25 mg/mL)
16.2 Storage and Handling
Store ZALTRAP vials in a refrigerator at 2 to 8°C (36 to 46°F). Keep the vials in the original outer carton to protect from light.

17 PATIENT COUNSELING INFORMATION
Advise patients:
• That ZALTRAP can cause severe bleeding. Advise patients to contact their health care provider for bleeding or symptoms of bleeding including lightheadedness.
• That ZALTRAP increases the risk of compromised wound healing. Instruct patients not to undergo surgery or procedures (including tooth extractions) without discussing first with their health care provider.
• That ZALTRAP can cause or exacerbate existing hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms.
• To notify the health care provider of severe diarrhea, vomiting, or severe abdominal pain.
• To notify their health care provider of fever or other signs of infection.
• Of an increased risk of arterial thromboembolic events.
• Of the potential risks to the fetus or neonate using ZALTRAP during pregnancy or nursing and of the need to use highly effective contraception in both males and females during and for at least 3 months following last dose of ZALTRAP therapy. Advise the patient to immediately contact the healthcare provider if they or their partner becomes pregnant during treatment with ZALTRAP.

Manufactured by:
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ZIV-FPLR-SL-OCT13 Rx Only