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.
**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)

**WARNINGS AND PRECAUTIONS**

- **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)

**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, and ALT increased, stomatitis, fatigue, thrombocytopenia, ALT increased, hypertension, weight decreased, decreased appetite, opisthotonos, abdominal pain, dysphonia, 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 (8.6)

See 17 for PATIENT COUNSELING INFORMATION

**CONTRAINDICATIONS**

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, 8.5)
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** Discontinue ZALTRAP. (5.10)

**REFERENCES**

This product is a copy of ZALTRAP (ziv-aflibercept) Injection for Intravenous Infusion

Initial U.S. Approval: 2012

**DOSAGE FORMS AND STRENGTHS**

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

**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/mL (25 mg/mL), 200 mg/8 mL (25 mg/mL) (3)**

**FULL PRESCRIBING INFORMATION: CONTENTS**

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

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WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, COMPROMISED WOUND HEALING

Hemorrhage: 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 GI events. Do not initiate or administer ZALTRAP to patients with severe hemorrhage (see Dosage and Administration (2.2), Warnings and Precautions (5.1)).

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 cancers populations), the incidence of GI perforation (all grades) was 0.8% for patients treated with ZALTRAP and 0.7% for patients treated with placebo/FOLFIRI (2% of patients treated with placebo/FOLFIRI were reported to have unhealed GI perforation). Do not use ZALTRAP in patients with GI perforation (see Adaptations and Administration (2.2), Warnings and Precautions (5.7)).

Compromised Wound Healing: 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 following major surgery and until the surgical wound is fully healed (see Dosage and Administration (2.2), Warnings and Precautions (5.3)).

1 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 (see Clinical Studies (14)).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Schedule

Administer ZALTRAP 4 mg per kg as an intravenous (IV) infusion over 1 hour every two weeks.

Discard ZALTRAP if the solution is discolored or cloudy or if the solution contains particles.

Sink vials prior to use. ZALTRAP is a clear, colorless to pale yellow solution. Do not use vials if the solution is discolored or cloudy or if the solution contains particles.

Monitor blood pressure every 2 weeks or more frequently as clinically indicated during treatment with ZALTRAP. Treat with appropriate antihypertensive 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)).

5.1 Hemorrhage

Patients treated with ZALTRAP have an increased risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. In patients with mCRC, bleeding/hemorrhage, has been reported in 38% of patients treated with ZALTRAP/FOLFIRI compared to 19% of patients treated with placebo/FOLFIRI. Grade 3–4 hemorrhagic events, including gastrointestinal hemorrhage, hematuria, and post-procedural hemorrhage, were reported in 3% of patients receiving ZALTRAP/FOLFIRI compared 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 0.7% for patients treated with placebo/FOLFIRI (2% of patients treated with placebo/FOLFIRI were reported to have unhealed GI perforation). Do not use ZALTRAP in patients with GI perforation (see Adaptations and Administration (2.2), Warnings and Precautions (5.7)).

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% of patients treated with ZALTRAP/FOLFIRI regimen and in none of the patients treated with placebo/FOLFIRI regimen. Suspend ZALTRAP for at least 4 weeks following major surgery and until the surgical wound is fully healed. For minor surgery such as central venous access port placement, biopsy, and tooth extraction, ZALTRAP may be initiated/resumed once the surgical wound is fully healed. Discontinue ZALTRAP in patients with compromised wound healing (see Dosage and Administration (2.2)).

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, enterocutaneous, 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 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 in patients with hypertensive crisis or hypertensive encephalopathy) occurred in 10% of patients treated with ZALTRAP/FOLFIRI. A higher incidence of Grade 3–4 hypertension, 54% had greater in 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 antihypertensive 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

Serious proteinuria, nephrotic syndrome, and thrombotic microangiopathy (TMA) occurred more frequently in patients treated with ZALTRAP/FOLFIRI. In patients with mCRC, proteinuria Grade 3 or 4 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 placebo/FOLFIRI compared to none of the patients treated with ZALTRAP/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 1 should undergo a 24-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 until 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 Neuropenia 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 occurred in 33% of patients treated with ZALTRAP/FOLFIRI compared to 7% of patients treated with placebo/FOLFIRI (see Adverse Reactions (6.1)). Grade 3–4 febrile neutropenia occurred in 4% of patients treated with ZALTRAP/FOLFIRI compared to 2% of patients treated with placebo/FOLFIRI. Grade 3–4 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 who are age 65 years or older as compared to patients younger than 65 years of age (see Genotoxic Use (8.5)). Monitor elderly patients closely for diarrhea.

5.10 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS, also known as posterior leukoencephalopathy, was reported in 0.5% of 7395 patients treated with ZALTRAP/FOLFIRI 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)]
- Fatigue [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 Neutrophilic 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 rates 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 every 2 weeks (N=611) or placebo (N=605) every two weeks (one cycle) in a randomized (1:1), double-blind, placebo-controlled Phase 3 study. Patients received a median of 9 cycles of ZALTRAP/FOLFIRI or 8 cycles of placebo/FOLFIRI.

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 (see Table 1).

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 (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 interrupted 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 are shown in Table 1.

Table 1 – Selected Adverse Reactions and Laboratory Findings in Study 1:

<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>All grades</td>
<td>Grades 3–4</td>
<td>All grades</td>
</tr>
<tr>
<td>Infestations and infestations</td>
<td>Uterine Tract Infection</td>
<td>6%</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Leukopenia</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>35%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased Appetite</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>3%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>9%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>11%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Epistaxis</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal Pain</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Rhinorrhea</td>
<td>2%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>Abdominal Pain</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>Abdominal Pain Upper</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Hemorrhoids</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Rectal Hemorrhage</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Proctalgia</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Palmar-Plantar Erythrodysesthesia Syndrome</td>
</tr>
<tr>
<td></td>
<td>Skin Hyperpigmentation</td>
<td>3%</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Proteinuria</td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine increased</td>
<td>19%</td>
</tr>
</tbody>
</table>

General disorders and administration site conditions

Fatigue | 39% | 8% |

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%).

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. Grade 3–4 VTE occurred in 8% of patients treated with ZALTRAP/FOLFIRI and in 6% of patients treated with placebo/FOLFIRI. Pulmonary embolism occurred in 5% of patients treated with ZALTRAP/FOLFIRI and 3.4% of patients treated with placebo/FOLFIRI.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. In patients with various cancers across 15 studies, 1.4% (41/2862) of patients tested positive for anti-product antibody (APA) at baseline. The incidence of APA development was 3.1% (53/1687) in patients receiving intravenous ziv-aflibercept and 1.7% (19/1134) in patients receiving placebo. Among patients who tested positive for APA and had sufficient samples for further testing, neutralizing antibodies were detected in 17 of 48 ziv-aflibercept-treated patients and in 2 of 40 patients receiving placebo.

The mean free ziv-aflibercept trough concentrations were lower in patients with positive neutralizing antibodies than in the overall population. The impact of neutralizing antibodies on efficacy and safety could not be assessed based on limited available data.

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 drug-drug interaction studies have been conducted for ZALTRAP. No clinically important pharmacokinetic drug-drug interactions were found between ziv-aflibercept and intravenous SN-38 or 5-FU, based on cross-study comparisons and population pharmacokinetic analyses.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with ZALTRAP in pregnant women. ZALTRAP was embryotoxic and teratogenic in rabbits at exposure levels lower than human exposures at the recommended dose, with increased incidences of external, visceral, and skeletal fetal malformations. ZALTRAP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Ziv-aflibercept produced embryo-fetal toxicity when administered every 3 days during organogenesis in pregnant rabbits at all intravenous doses tested, ≥ 3 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation losses and external (including anasarca, umbilical hernia, diaphragmatic hernia and gastrochisis, cleft palate, exstrophy, and atresia), visceral (in the heart, great vessels, and arteries), and skeletal fetal malformations (including fused vertebrae, sternebrae, and ribs; supernumerary arches and ribs, and incomplete ossification). Administration of the 3 mg per kg dose to rabbits resulted in systemic exposure (AUC) that was approximately 30% of the AUC in patients at the recommended dose. The incidence and severity of fetal anomalies increased with increasing dose.

8.3 Nursing Mothers

It is not known whether ZALTRAP is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ZALTRAP, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 611 patients with mCRC, patients treated with ZALTRAP/FOLFIRI, 205 (34%) were 65 years or older, and 33 (5%) were 75 years or older. Elderly patients ≥65 years of age experienced higher incidences (≥5%) of diarrhea, dizziness, asthenia, weight decrease, and dehydration when compared to younger patients. Monitor elderly patients more closely for diarrhea and dehydration (see Warnings and Precautions (5.9)).

The effect of ZALTRAP on overall survival was similar in patients <65 years old and ≥65 years old who received ZALTRAP/FOLFIRI.

8.6 Hepatic Impairment

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of ziv-aflibercept.
Based on a population PK analysis with data from 1507 patients, ziv-aflibercept exposure in patients with mild and moderate hepatic impairment was similar to those in patients with normal hepatic function [see Clinical Pharmacology (12.3)]. There are no data available for patients with severe hepatic impairment.

8.7 Renal Impairment

No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of ziv-aflibercept. Based on a population PK analysis with data from 1507 patients, ziv-aflibercept exposure in patients with mild, moderate, and severe renal impairment were similar to those in patients with normal renal function [see Clinical Pharmacology (12.3)].

8.8 Females and Males of Reproductive Potential

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 reversible within 18 weeks after cessation of treatment. Females and males of reproductive potential should use highly effective contraceptive during and up to a minimum of 3 months after the last dose of treatment.

10 OVERDOSAGE

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 protein molecular weight of 97 kilodaltons (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 (25 mg/mL). 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 protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa.

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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.

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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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Bridgewater, NJ 08807,
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