CODING AND BILLING INFORMATION FOR ZALTRAP®

ZALTRAP is indicated in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI) for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen. ZALTRAP may be administered in various sites of service, including physician offices and hospitals. Please note that coding requirements will vary by setting and payer. Multiple code sets are required to accurately and adequately report services associated with ZALTRAP to payers.

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.

Reporting of diagnosis codes needs to be done to the highest level of specificity including 4th and 5th digit reporting as appropriate. Certain diagnoses may require review of complete code listing. Please consult primary coding references for the full code descriptions.

ICD-9-CM, CPT, and/or HCPCS codes should be selected and used by physicians based upon the code or codes that most accurately describe the diagnosis and the procedure performed and that is consistent with the requirements of any applicable health insurers. To support compliance with insurer requirements, physicians should contact local, public, or private health insurance carriers or advisors for their choice in determining the appropriate code for the services provided.

Sanofi-aventis cannot and does not guarantee that use of any code(s) will ensure coverage or payment at any level.

Please see complete Important Safety Information on pages 6–11 and accompanying full Prescribing Information, including BOXED WARNING.
COVERAGE
For qualified Medicare beneficiaries, ZALTRAP® (ziv-aflibercept) is eligible for coverage under the Medicare Part B benefit. ZALTRAP claims will be processed by Part A/B Medicare Administrative Contractors (MACs) for physician office and hospital sites of service, Carriers (physician office) or Fiscal Intermediaries (hospitals). Medicare Advantage plans will most likely cover ZALTRAP under a medical benefit. Private payers and Medicaid will likely cover ZALTRAP under the medical benefit—as they do other physician-administered products—but there are some scenarios where this may not always be the case.

ZALTRAP® (ziv-aflibercept) INJECTION FOR INTRAVENOUS INFUSION
ZALTRAP may be identified by a Healthcare Common Procedure Coding System (HCPCS) Level II code and by a National Drug Code (NDC).

HCPCS Level II codes include J-codes and C-codes. The following codes should be utilized for billing:

<table>
<thead>
<tr>
<th>HCPCS Level II</th>
<th>Site of Care</th>
<th>Payer</th>
</tr>
</thead>
<tbody>
<tr>
<td>J9400</td>
<td>Injection, ziv-aflibercept, 1 mg</td>
<td>Physician Office, Medicare, Commercial, Most Medicaid</td>
</tr>
<tr>
<td>C9296</td>
<td>Injection, ziv-aflibercept, 1 mg</td>
<td>Hospital Outpatient, Medicare, Most Commercial, Medicaid</td>
</tr>
</tbody>
</table>

When reporting drugs by J-code, include drug-identifying information in the Comment or Remarks areas on the Centers for Medicare & Medicaid Services claim form. Please note that requirements may vary by payer (eg, certain payers require billing for both drug amount administered and drug amount wasted):

- ZALTRAP® (ziv-aflibercept)
- IV infusion—1 hour
- Drug strength and dosage
- 11-digit NDC
- Drug amount administered
- Number of vials used

Please note: This document is an abbreviated reference for informational purposes only and subject to change. Providers should exercise independent clinical judgment when submitting claims and selecting codes (eg, use the codes that most accurately describe the procedure performed and that are consistent with the requirements of any applicable health insurers). To support compliance with insurer requirements, providers should contact local, public, or private health insurers to determine the appropriate codes for the services provided. Sanofi-aventis cannot and does not guarantee that use of any code(s) will ensure coverage or payment at any level.

PRODUCT CODES

An NDC may be required for ZALTRAP® (ziv-aflibercept) to further identify the drug. An NDC is a universal, unique, three-segment number that identifies drugs by manufacturer, drug formulation/dosage/strength, and package size. The Health Insurance Portability and Accountability Act (HIPAA) format for electronic claim submission requires the NDC to be reported in an 11-digit format. Check payer claim submission requirements and guidance for accurate reporting of the NDC and other identifiers.

<table>
<thead>
<tr>
<th>NDC</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>00024-S840-01 (160 mg/4 mL)</td>
<td>ZALTRAP is supplied in either 5 mL or 10 mL glass vial containing 100 mg or 200 mg of ziv-aflibercept, respectively, as a sterile, preservative-free, non-pyrogenic, clear, colorless to pale yellow solution at a concentration of 25 mg/mL.</td>
</tr>
<tr>
<td>00024-S841-01 (200 mg/8 mL)</td>
<td></td>
</tr>
</tbody>
</table>

Please note that there may be differences among payers in requirements for billing with J-codes. Please check with your payer or Sanofi Patient Connection™ for specific billing details.

DIAGNOSIS CODES

The medical necessity of ZALTRAP, in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI), for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen can be documented through the use of appropriate ICD-9-CM diagnosis codes. Medical necessity and diagnosis requirements may vary among payers, so it is best to consult payer guidelines for information regarding ICD-9-CM code reporting. ICD-9-CM codes 153.0–153.9, 154.0, 154.1, 154.2, 154.3, and 154.8 may be most appropriate for ZALTRAP. Providers should use their independent clinical judgment when selecting codes and submitting claims.

Please see complete Important Safety Information on pages 6–11 and accompanying full Prescribing Information, including BOXED WARNING.
**DRUG ADMINISTRATION CODES**

Physician offices and hospital outpatient facilities use Current Procedural Terminology (CPT®) codes to report the administration of ZALTRAP® (ziv-aflibercept). Some hospital inpatient departments may itemize CPT codes on claim forms for their own internal tracking purposes. CPT code 96413 is generally considered to be the most appropriate CPT code to report a 1-hour IV infusion of ZALTRAP. Administration codes for these agents vary by payer.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>96413</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy administration, IV infusion technique: up to 1 hour, single or initial substance/drug</td>
<td></td>
</tr>
</tbody>
</table>

**IMPORTANT SAFETY INFORMATION FOR ZALTRAP® (ziv-aflibercept) INJECTION FOR INTRAVENOUS INFUSION**

- GI perforation including fatal GI perforation can occur in patients receiving ZALTRAP.
  - Across three clinical trials (colorectal, pancreatic, and lung cancer), GI perforation (all grades/Grade 3-4) occurred in 0.8%/0.8% of ZALTRAP patients and 0.3%/0.2% for placebo patients.
  - Monitor patients for signs and symptoms of GI perforation. Discontinue ZALTRAP in patients who experience GI perforation.
- ZALTRAP impairs wound healing in animal models. Grade 3 compromised wound healing occurred in 2 patients (0.3%) treated with ZALTRAP/FOLFIRI and none of the patients treated with placebo/FOLFIRI.
  - Discontinue ZALTRAP in patients with compromised wound healing.
  - Suspend ZALTRAP for at least 4 weeks prior to elective surgery and do not initiate/resume ZALTRAP until at least 4 weeks after major surgery and 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.

Please see complete Important Safety Information on pages 6–11 and accompanying full Prescribing Information, including BOXED WARNING.

**HOSPITAL CODING (inpatient)**

Health care professionals who provide ZALTRAP® (ziv-aflibercept) to Medicare patients in a hospital may report the administration of ZALTRAP using the following ICD-9-CM procedure code (inpatient):

<table>
<thead>
<tr>
<th>ICD-9-CM Procedure Code</th>
<th>99.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection or infusion of cancer chemotherapeutic substance</td>
<td></td>
</tr>
</tbody>
</table>

**REVENUE CODES**

UB revenue codes categorize hospital services by cost or revenue center, which can then be used for cost-reporting purposes. Revenue code 0250 is generally used in the inpatient setting. Revenue code 0636 is used in the hospital outpatient setting for all pharmacy supplies that are separately payable.

<table>
<thead>
<tr>
<th>Revenue Codes</th>
<th>0250</th>
<th>0636</th>
<th>0335</th>
<th>0510</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy, general</td>
<td>Drug – Inpatient</td>
<td>Drugs requiring detailed coding</td>
<td>Drug – Outpatient</td>
<td>Chemotherapy IV</td>
</tr>
<tr>
<td></td>
<td>IV infusion</td>
<td>Clinic, general</td>
<td>Clinic visit</td>
<td></td>
</tr>
</tbody>
</table>

**IMPORTANT SAFETY INFORMATION FOR ZALTRAP® (ziv-aflibercept) INJECTION FOR INTRAVENOUS INFUSION**

- Fistula formation involving GI and non-GI sites occurs at a higher incidence in patients treated with ZALTRAP. Fistulas (anal, enterovesical, enterocutaneous, colovaginal, intestinal sites) were reported in 1.5% (9/611) of ZALTRAP/FOLFIRI treated patients and 0.5% (3/605) of placebo/FOLFIRI patients. Grade 3 GI fistula formation occurred in 2 patients treated with ZALTRAP (0.3%) and 1 placebo-treated patient (0.2%). Discontinue ZALTRAP therapy in patients who develop fistula.

Please see complete Important Safety Information on pages 6–11 and accompanying full Prescribing Information, including BOXED WARNING.
ZALTRAP® (ziv-aflibercept) is indicated in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI) for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

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.
  - Bleeding/hemorrhage (all grades) occurred in 38% of ZALTRAP/FOLFIRI patients vs. 19% of placebo/FOLFIRI patients. Grade 3-4 hemorrhagic events, including GI hemorrhage, hematuria, and post-procedural hemorrhage, occurred in 3% of ZALTRAP/FOLFIRI patients vs. 1% of placebo/FOLFIRI patients. Severe intracranial hemorrhage and pulmonary hemorrhage/hemoptysis including fatal events have occurred in patients receiving ZALTRAP.

- GI perforation including fatal GI perforation can occur in patients receiving ZALTRAP.
  - Across three clinical trials (colorectal, pancreatic, and lung cancer), GI perforation (all grades/Grade 3-4) occurred in 0.8%/0.8% of ZALTRAP patients and 0.3%/0.2% for placebo patients.
  - Monitor patients for signs and symptoms of GI perforation. Discontinue ZALTRAP in patients who experience GI perforation.

Please see complete Important Safety Information on pages 6–11 and accompanying full Prescribing Information, including BOXED WARNING.

IMPORTANT SAFETY INFORMATION FOR ZALTRAP® (ziv-aflibercept) INJECTION FOR INTRAVENOUS INFUSION (cont’d)

- ZALTRAP impairs wound healing in animal models. Grade 3 compromised wound healing occurred in 2 patients (0.3%) treated with ZALTRAP/FOLFIRI and none of the patients treated with placebo/FOLFIRI.
  - Discontinue ZALTRAP in patients with compromised wound healing.
  - Suspend ZALTRAP for at least 4 weeks prior to elective surgery and do not initiate/resume ZALTRAP until at least 4 weeks after major surgery and 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.

- Fistula formation involving GI and non-GI sites occurs at a higher incidence in patients treated with ZALTRAP. Fistulas (anal, enterovesical, enterocutaneous, colovaginal, intestinal sites) were reported in 1.5% (9/611) of ZALTRAP/FOLFIRI treated patients and 0.5% (3/605) of placebo/FOLFIRI patients. Grade 3 GI fistula formation occurred in 2 patients treated with ZALTRAP (0.3%) and 1 placebo-treated patient (0.2%). Discontinue ZALTRAP therapy in patients who develop fistula.

- An increased risk of Grade 3-4 hypertension has been observed in patients receiving ZALTRAP.
  - 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% treated with ZALTRAP/FOLFIRI. Grade 4 hypertension (hypertensive crisis) was reported in 1 patient (0.2%) treated with ZALTRAP/FOLFIRI. Of patients treated with ZALTRAP/FOLFIRI who developed Grade 3-4 hypertension, 54% had onset during the first two cycles of treatment.
  - Monitor blood pressure at least every two weeks, treat with appropriate anti-hypertensive therapy, and continue monitoring blood pressure regularly during ZALTRAP treatment. 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 or hypertensive encephalopathy.
IMPORTANT SAFETY INFORMATION FOR ZALTRAP® (ziv-aflibercept)
INJECTION FOR INTRAVENOUS INFUSION (cont’d)

• Arterial thromboembolic events (ATE), including transient ischemic attack, cerebrovascular accident, and angina pectoris, occurred more frequently in patients who have received ZALTRAP. ATE occurred in 2.6% of ZALTRAP/FOLFIRI patients and 1.7% of placebo/FOLFIRI patients. 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.

• Severe proteinuria, nephrotic syndrome, and thrombotic microangiopathy (TMA) occurred more frequently in patients treated with ZALTRAP.
  – Proteinuria was reported in 62% of ZALTRAP/FOLFIRI patients compared to 41% of placebo/FOLFIRI patients. Grade 3-4 proteinuria occurred in 8% of ZALTRAP/FOLFIRI patients compared to 1% of placebo/FOLFIRI patients. Nephrotic syndrome occurred in 2 patients (0.5%) 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. Obtain a 24-hour urine collection in patients with a dipstick of ≥2+ for protein or UPCR >1.
  – 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.
  – Grade 3-4 neutropenia occurred in 37% of ZALTRAP/FOLFIRI patients compared to 30% of placebo/FOLFIRI patients. Grade 3-4 febrile neutropenia occurred in 4% of ZALTRAP/FOLFIRI patients compared to 2% of placebo/FOLFIRI patients. Grade 3-4 neutropenic infection/sepsis occurred in 1.5% of ZALTRAP/FOLFIRI patients compared to 1.2% of placebo/FOLFIRI patients.
  – Monitor CBC with differential count at baseline and prior to initiation of each cycle of ZALTRAP. Delay administration of ZALTRAP/FOLFIRI until neutrophil count is ≥1.5 x 10⁹/L.

• Incidence of severe diarrhea and dehydration is increased in patients treated with ZALTRAP/FOLFIRI.
  – Grade 3-4 diarrhea was reported in 19% of ZALTRAP/FOLFIRI patients compared to 8% of placebo/FOLFIRI patients. Grade 3-4 dehydration was reported in 4% of ZALTRAP/FOLFIRI patients compared to 1% of placebo/FOLFIRI patients.
  – The incidence of diarrhea is increased in patients ≥65 years of age compared to patients <65 years of age. Monitor closely.

• RPLS (also known as posterior reversible encephalopathy syndrome) was reported in 0.5% of 3795 patients treated with ZALTRAP monotherapy or in combination with chemotherapy. Confirm 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.

Please see complete Important Safety Information on pages 6–11 and accompanying full Prescribing Information, including BOXED WARNING.
IMPORTANT SAFETY INFORMATION FOR ZALTRAP® (ziv-aflibercept)
INJECTION FOR INTRAVENOUS INFUSION (cont’d)

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.

PREGNANCY AND NURSING MOTHERS

- ZALTRAP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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.

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

Please see complete Important Safety Information on pages 6–11 and accompanying full Prescribing Information, including BOXED WARNING.
Sanofi Patient Connection is committed to patient support
The Sanofi Patient Connection program offers toll-free provider reimbursement and patient-assistance support for ZALTRAP® (ziv-aflibercept). Services include:

- Benefit verification
- Prior authorization assistance
- Billing and coding support
- Claims and appeals assistance
- Patient Assistance Program
- Resource connections

If you have any coding or billing questions, please contact Sanofi Patient Connection at:
Phone: 1-888-847-4877
Fax: 1-888-847-1797
Website: www.visitSPConline.com
Hours of operation: Monday–Friday, 9 AM–8 PM ET

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.

Please see complete Important Safety Information on pages 6–11 and accompanying full Prescribing Information, including BOXED WARNING.

In the U.S. ZALTRAP is a registered trademark of Regeneron Pharmaceuticals, Inc.
CPT is a registered trademark of the American Medical Association.
Patient Connection is a trademark of sanofi-aventis U.S. LLC.

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US.AFL.14.01.009 01/14
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)

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)

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

Adverse Reactions

- Hemorrhage: Severe, frequent, 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)

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)

Drug Interactions

- Pregnancy
- Nursing Mothers
- Pediatric Use
- Geriatric Use
- Hepatic Impairment
- Renal Impairment
- Females and Males of Reproductive Potential

Overdosage

Revised: 10/2013

Full Prescribing Information: Contents

1 Indications and Usage
2 Dosage and Administration
3 Dosage Forms and Strengths
4 Contraindications
5 Warnings and Precautions
6 Adverse Reactions
7 Drug Interactions
8 Use in Specific Populations
9 Other Information
10 Overdosage
11 Description
12 Clinical Pharmacology
13 Nonclinical Toxicology
14 Clinical Studies
15 How Supplied/Storage and Handling
16 Patient Counseling Information

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

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/heamorrhage, including fatal events, has 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 0.3% for patients treated with placebo. Grade 3–4 GI perforation occurred in 0.8% of 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 placebo-treated patients (0.5%) treated with ZALTRAP/FOLFIRI regimen and in none of the patients treated with placebo/FOLFIRI regimen. Grade 4 fistula for at least 4 weeks following major surgery occurred in 2 patients (0.4%) for ZALTRAP/FOLFIRI for at least 4 weeks following major surgery and until 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 (anastomotic, enterocutaneous, enterocutaneous fistula, colovaginal, intestinal stoma) 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 placebo-treated patients (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 an additional antihypertensive medication) occurred in 34% of patients during the first two cycles of treatment. In patients with mCRC, Grade 3–4 hypertension, 34% 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 cystoscopic hypertension [see Dosage and Administration (2.2)].

5.6 Arterial Thromboembolic Events

Arterial thromboembolic events (ATE) include transient ischemic attack, cerebrovascular accident, and aneurysm, 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/FOLFIRI compared to placebo/FOLFIRI. In patients with mCRC, Grade 3–4 proteinuria occurred in 42% of patients treated with ZALTRAP/FOLFIRI compared to 8% of patients treated with placebo/FOLFIRI. Grade 3–4 proteinuria occurred in 8% of patients treated with ZALTRAP/FOLFIRI compared 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 and 1 patient (0.1%) treated with placebo/FOLFIRI. Grade 3–4 neutropenia/sepsis occurred in 1.5% of patients treated with ZALTRAP/FOLFIRI and 1.2% of 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 1.0 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 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 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 occurred in 32% of patients treated with ZALTRAP/FOLFIRI compared to 30% 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 neutropenic 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 10⁹/L. If recurrent, suspend ZALTRAP until neutrophil count is at or above 1.5 x 10⁹/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 Geriatric Use (8.5)]. Monitor elderly patients closely for diarrhea.

5.10 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Onyx-015, also known as prostratin, as reported in 0.6% of 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 Warnings, Warnings and Precautions (5.1)]
- **Gastrointestinal Perforation** [see Boxed Warnings, Warnings and Precautions (5.2)]
- **Compromised Wound Healing** [see Boxed Warnings, Warnings and Precautions (5.3)]
- **Fatality 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 Neutrophilic Complications** [see Warnings and Precautions (5.8)]
- **Diabetes 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 (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 8 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, proteinuria, AST increased, stomatitis, fatigue, thrombocytopenia, ALT increased, hypertension, weight decreased, decreased appetite, epistaxis, abdominal pain, dyspnea, serum creatinine increased, and headache (see Table 1).

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 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, proteinuria, and proteinuria.

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

<table>
<thead>
<tr>
<th>Preferred Term (%)</th>
<th>Placebo/FOLFIRI (N=605)</th>
<th>ZALTRAP/FOLFIRI (N=611)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary System Organ Class</strong></td>
<td>All grades</td>
<td>Grades 3-4</td>
</tr>
<tr>
<td>Inflections and infestations</td>
<td>6%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>72%</td>
<td>12%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>57%</td>
<td>30%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35%</td>
<td>2%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>24%</td>
<td>2%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>24%</td>
<td>2%</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>24%</td>
<td>2%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>25%</td>
<td>0%</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>9%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Oropharyngeal Pain</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>33%</td>
<td>5%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>33%</td>
<td>5%</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Rectal Hemorrhage</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Proctalgia</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Palmar-Plantar Erythrodysesthesia Syndrome</td>
<td>4%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Skin Hypertigmentation</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>41%</td>
<td>1%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>19%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

#### General disorders and administration site conditions

**Fatigue**

39% | 8% | 48% | 13% |

**Anemia**

13% | 3% | 18% | 5% |

**Investigations**

AST increased

54% | 2% | 62% | 3% |

ALT increased

39% | 2% | 50% | 3% |

**Weight decreased**

14% | 0.8% | 32% | 3% |

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%).

#### 6.2 Immunogenicity

Anti-ZALTRAP antibodies in patients with all therapeutic proteins, there is a potential for immunogenicity. In patients with various cancers across 15 studies, 1.4% (41/2826) 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% (191/1134) 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, ectrodactyly, 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.

**8.2 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.

**8.3 Pediatric Use**

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

**8.4 Geriatric Use**

The effect of ZALTRAP on overall survival was similar in patients ≥65 years old and ≥65 years old who received ZALTRAP/FOLFIRI. No dose adjustment of ZALTRAP is recommended for patients greater than or equal to 65 years of age.

**8.5 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, moderate, and severe hepatic impairment were similar to those in patients with normal renal function. Based on a population PK analysis with data from 1507 patients, ziv-aflibercept exposure in patients A total of 1226 patients were randomized (1:1) to receive either ZALTRAP (N=612; 4 mg per kg as a 1 hour intravenous infusion on day 1) or placebo (N=614), in combination with 5-fluorouracil plus irinotecan (FOLFIRO; irinotecan 180 mg per m² IV infusion over 90 minutes and leucovorin (5 mg/m²) 400 mg per m² IV intravenous infusion over 2 hours at the same time on day 1 using a Y-line, followed by 2-FU 400 mg per m² IV intravenous bolus, followed by 5-FU 2400 mg per m² continuous intravenous infusion over 46-hours). The treatment cycles on both arms were repeated every 2 weeks. Patients were treated until disease progression or unacceptable toxicity. The primary efficacy endpoint was overall survival. Treatment assignment was stratified by the ECOG performance status (0 versus 1 versus 2) and according to prior therapy with bevacizumab (yes or no).

Demographics characteristics were similar between treatment arms. Of the 1226 patients randomized, the median age was 61 years, 59% were men, 87% were White, 3.5% were Black, and 98% had a baseline ECOG performance status (PS) of 0 or 1. Among the 1226 randomized patients, 89% and 90% of patients treated with placebo/FOLFIRI and ZALTRAP/FOLFIRI, respectively, received prior oxaliplatin-based combination chemotherapy in the metastatic advanced setting. A total of 345 patients (28%) received bevacizumab in combination with the prior oxaliplatin-based treatment. The median number of cycles of ZALTRAP/FOLFIRI regimen versus the placebo/FOLFIRI regimen are summarized in Figure 1 and Table 2.

**Figure 1 — Overall survival (months) — Kaplan-Meier curves by treatment group**

**Table 2 Main efficacy outcome measures**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Overall Survival</th>
<th>Median PFS (95% CI)</th>
<th>Stratified Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/FOLFIRI (N=614)</td>
<td>460 (74.9%)</td>
<td>12.05 (11.07 to 13.08)</td>
<td>0.817 (0.714 to 0.935)</td>
</tr>
<tr>
<td>ZALTRAP/FOLFIRI (N=612)</td>
<td>403 (65.8%)</td>
<td>13.50 (12.52 to 14.95)</td>
<td>0.0032</td>
</tr>
<tr>
<td>Stratified Log-Rank test p-value</td>
<td>0.0032</td>
<td>0.0007</td>
<td></td>
</tr>
<tr>
<td>Progression Free Survival (PFS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events, n (%)</td>
<td>454 (73.9%)</td>
<td>393 (64.2%)</td>
<td></td>
</tr>
<tr>
<td>Median PFS (95% CI) (months)</td>
<td>4.67 (2.41 to 5.36)</td>
<td>6.90 (5.17 to 7.20)</td>
<td></td>
</tr>
<tr>
<td>Stratified Hazard ratio (95% CI)</td>
<td>0.758 (0.661 to 0.869)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratified Log-Rank test p-value</td>
<td>0.0007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Response Rate (CR+PR) (95% CI)</td>
<td>11.1 (8.5 to 13.8)</td>
<td>19.8 (16.4 to 23.2)</td>
<td></td>
</tr>
<tr>
<td>Stratified Cochrane-Mantel-Haenszel test p-value</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PFS** (based on tumor assessment by the IRC): Significance threshold is set to 0.0001.

**FStratified on ECOG Performance Status (0 vs 1 vs 2) and Prior Bevacizumab (yes vs no)**

**Overall objective response rate by IRC**

Planned subgroup analyses for overall survival based on stratification factors at randomization yielded an HR of 0.98 (95% CI: 0.68 to 1.01) in patients who received prior bevacizumab and an HR of 0.79 (95% CI 0.67 to 0.98) in patients without prior bevacizumab exposure.

**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 2004-5840-01: containing one (1) single-use vial of 100 mg per 4 mL (25 mg/mL) NDC 2004-5840-03: containing three (3) single-use vials of 100 mg per 4 mL (25 mg/mL) NDC 2004-5841-01: 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 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.