PRODUCT INFORMATION

ZALTRAP®

NAME OF MEDICINE

AUSTRALIAN APPROVED NAME

Aflibercept (rch)

CHEMICAL STRUCTURE

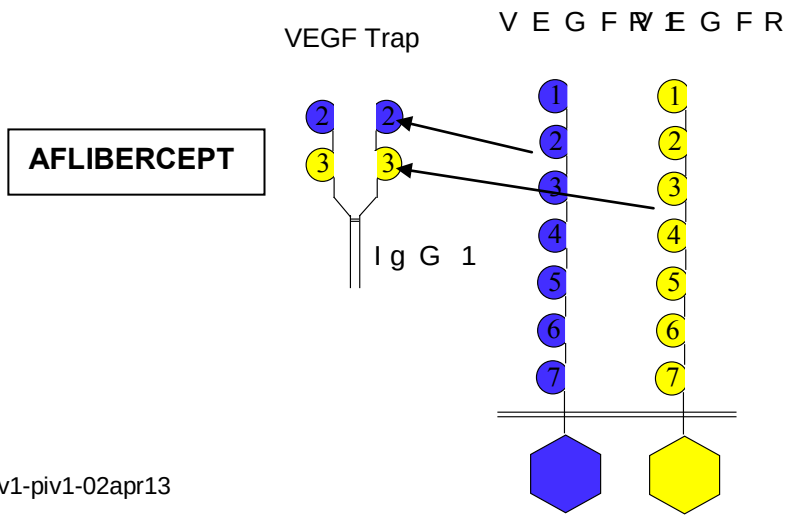
Aflibercept is a recombinant protein consisting of sequences derived from human vascular endothelial growth factor (VEGF) receptor extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG1).

The extracellular domain sequences come from two different VEGF receptors, VEGFR1 (also known as Flt-1) and VEGFR2 (also known as KDR or Flk-1). Each of the VEGF receptors are composed of seven immunoglobulin (Ig) domains in their extracellular regions, with Ig domains 2 and 3 contributing the majority of the binding energy for VEGF.

Thus the amino acid sequence structure of aflibercept comprises Ig domain 2 from VEGFR1, fused to Ig domain 3 from VEGFR2, which is in turn fused to the Fc domain of IgG1.

There are no extraneous linker sequences between any of the peptide domains. The presumptive Ig domain structure of aflibercept is provided in Figure 1.

Figure 1 - Structure of aflibercept



MOLECULAR FORMULA

Aflibercept molecular formula (without glycosylation) is $C_{4318}H_{6788}N_{1164}O_{1304}S_{32}$.

MOLECULAR WEIGHT

115 kDa

CHEMICAL NAME

1. Vascular endothelial growth factor receptor type VEGFR-1 (synthetic human immunoglobulin domain 2 fragment) fusion protein with vascular endothelial growth factor receptor type VEGFR-2 (synthetic human immunoglobulin domain 3 fragment) fusion protein with immunoglobulin G1 (synthetic Fc fragment), dimer.

2. des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2- (206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer.

CAS REGISTRY NUMBER

862111-32-8

DESCRIPTION

Aflibercept, also known as VEGF-TRAP in the scientific literature, 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. Aflibercept is produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) K-1 mammalian expression system. 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.

Excipients: Sucrose, sodium chloride, citric acid monohydrate, sodium citrate (dihydrate), polysorbate 20, sodium phosphate dibasic (heptahydrate), sodium phosphate monobasic

monohydrate, sodium hydroxide and/or hydrochloric acid (for pH adjustment), and water for injections.

PHARMACOLOGY

PHARMACODYNAMICS

Mechanism of Action

Vascular endothelial growth factor A and B (VEGF-A, VEGF-B), and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF-A acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF and VEGF-B bind only to VEGFR-1, which is also present on the surface of leukocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF is also linked to pathological neovascularisation and recruitment of inflammatory cells into tumours.

Aflibercept acts as a soluble decoy receptor that binds to VEGF-A, with higher affinity than its native receptors, as well as the related ligands PlGF and VEGF B. By acting as a ligand trap, aflibercept prevents binding of endogenous ligands to their cognate receptors and thereby blocks receptor mediated signaling.

Aflibercept blocks the activation of VEGF receptors and the proliferation of endothelial cells, thereby inhibiting the growth of new vessels that supply tumours with oxygen and nutrients.

Aflibercept 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 PlGF (K_D of 39 pM for PlGF-2), and to human VEGF-B (K_D of 1.92 pM) to form a stable, inert complex which has no detectable biological activity.

Pharmacodynamic effects

Administration of aflibercept to mice bearing xenotransplant or allotransplant tumours inhibited the growth of various cancer types.

PHARMACOKINETICS

Both non-clinical and clinical pharmacokinetics have been evaluated for aflibercept.

A population pharmacokinetic analysis was performed with data from 1,507 patients with various types of advanced malignancies, who had received aflibercept as a single agent or in combination at doses ranging from 2 to 9 mg/kg administered every 2 to 3 weeks as a 1-hour intravenous infusion. Plasma concentrations of free and bound aflibercept were measured using specific enzyme-linked immunosorbent assay (ELISA) methods.

Absorption

In preclinical tumour models, biologically active doses of aflibercept correlated with those necessary to produce circulating concentrations of free aflibercept in excess of VEGF-bound aflibercept. Circulating concentrations of VEGF-bound aflibercept increase with the aflibercept dose until most available VEGF is bound. Further increases in the aflibercept dose result in dose-related increases in circulating free aflibercept concentrations but only small further increases in the VEGF-bound aflibercept concentration.

In patients, Zaltrap is administered at a dose of 4 mg/kg intravenously every two weeks for which there is an excess of circulating free aflibercept compared to VEGF-bound aflibercept.

At the recommended dose regimen of 4 mg/kg every two weeks, concentration of free aflibercept was near steady-state levels by the second cycle with essentially no accumulation (accumulation ratio of 1.2 at steady-state compared to the first administration).

Distribution

The volume of distribution of free aflibercept at steady-state is 8 litres.

Metabolism

No metabolism studies have been conducted with aflibercept since it is a protein. Aflibercept is expected to degrade to small peptides and individual amino acids.

Elimination

Free aflibercept is primarily cleared by binding to endogenous VEGF to form a stable, inert complex. As with other large proteins, both free and bound aflibercept, are expected to be cleared more slowly, by other biological mechanisms, such as proteolytic catabolism. VEGF-bound aflibercept is eliminated without either an appreciable extent of reversible dissociation or the formation of higher order immunocomplexes.

At doses greater than 2 mg/kg, free aflibercept clearance was 1.0 L/day with a terminal half-life of 6 days.

High molecular weight proteins are not cleared by the renal route, therefore renal elimination of aflibercept is expected to be minimal.

Special populations

Gender

Despite differences in free aflibercept clearance and volume of distribution in males and females, no gender-related difference in aflibercept exposure was seen at the 4 mg/kg dose in the pivotal study.

Elderly

There was no effect of age on the pharmacokinetics of free aflibercept.

Race

There was no effect of ethnic groups/race on the pharmacokinetics of free aflibercept.

Weight

Weight had an effect on free aflibercept clearance and volume of distribution resulting in a 29% increase in aflibercept exposure in patients weighing ≥100 kg.

Hepatic impairment

There have been no formal studies with aflibercept in patients with hepatic impairment. In a population pharmacokinetic analysis with data from 1,507 patients with various types of advanced malignancies receiving aflibercept with or without chemotherapy, 63 patients with mild hepatic impairment (total bilirubin >1.0x – 1.5x ULN and any AST) and 5 patients with moderate hepatic impairment (total bilirubin >1.5x – 3x ULN and any AST) were treated with aflibercept. In these mild and moderate hepatic impairment patients, there was no effect on clearance of aflibercept. There are no data available for patients with severe hepatic impairment (total bilirubin >3x ULN and any AST).

Renal impairment

There have been no formal studies with aflibercept in patients with renal impairment. A population pharmacokinetic analysis was conducted with data from 1,507 patients with various types of advanced malignancies receiving aflibercept with or without chemotherapy. This population included; 549 patients with mild renal impairment (CLCR between 50-80 ml/min), 96 patients with moderate renal impairment (CLCR between 30-50 ml/min), and 5 patients with

severe renal impairment (CLCR <30 ml/min). This population pharmacokinetic analysis revealed no differences in systemic exposure (AUC) of free aflibercept amongst patients with various degrees of renal impairment at the 4 mg/kg dose of aflibercept.

CLINICAL TRIALS

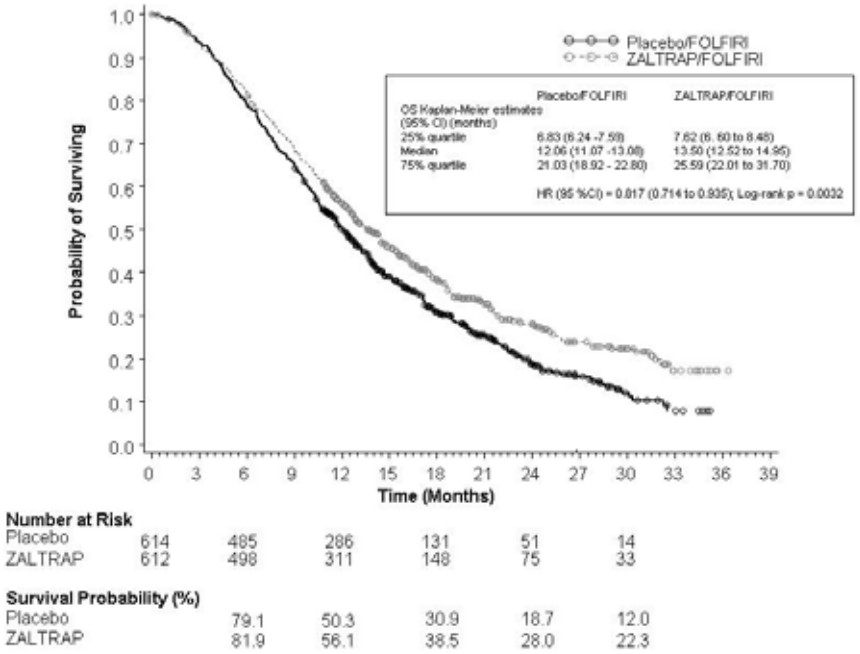
Clinical efficacy and safety

The efficacy and safety of Zaltrap were evaluated in a randomised, double-blind, placebo-controlled study (VELOUR) in patients with metastatic colorectal cancer who had previously been treated with an oxaliplatin-based treatment with or without prior bevacizumab. A total of 1,226 patients were randomised (1:1) to receive either Zaltrap (N=612; 4 mg/kg as a 1 hour intravenous infusion on day 1) or placebo (N=614), in combination with 5-fluouracil plus irinotecan [FOLFIRI: irinotecan 180 mg/m^2 intravenous infusion over 90 minutes and folinic acid (dl racemic) 400 mg/m² intravenous infusion over 2 hours at the same time on day 1 using a Y-line, followed by 5-FU 400 mg/m² intravenous bolus, followed by 5-FU 2,400 mg/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 were well balanced between the treatment arms (age, race, ECOG performance status, and prior bevacizumab status). Of the 1,226 patients randomised in the study, the median age was 61 years, 58.6% were male, and 97.8% had a baseline ECOG performance status (PS) of 0 or 1. Among the 1,226 randomised patients, 89.4% and 90.2% of patients treated with placebo/FOLFIRI and Zaltrap/FOLFIRI regimen, respectively, received prior oxaliplatin-based combination chemotherapy in the metastatic/advanced setting. Approximately 10% of patients (10.4% and 9.8% of patients treated with placebo/FOLFIRI and Zaltrap/FOLFIRI regimens, respectively) received prior oxaliplatin-based adjuvant chemotherapy and progressed on or within 6 months of completion of adjuvant chemotherapy. Oxaliplatin-based regimens were administered in combination with bevacizumab in 373 patients (30.4%).

Overall efficacy results for the Zaltrap/FOLFIRI regimen versus the placebo/FOLFIRI regimen are summarised in Figure 2 and Table 1.

Figure 2 - Overall survival (months) – Kaplan-Meier curves by treatment group – ITT population



Number at Risk

Placebo	614	485	286	131	51	14
ZALTRAP	612	498	311	148	75	33

Survival Probability (%)

Placebo	79.1	50.3	30.9	18.7	12.0
ZALTRAP	81.9	56.1	38.5	28.0	22.3

Table 1 - Main efficacy endpoints[a] – ITT population

	Placebo/FOLFIRI (N=614)	Zaltrap/FOLFIRI (N=612)
Overall Survival		
Number of death events, n (%)	460 (74.9%)	403 (65.8%)
Median overall survival (95% CI) (months)	12.06 (11.07 to 13.08)	13.50 (12.52 to 14.95)
Stratified hazard ratio (95% CI)	0.817 (0.714 to 0.935)	
Stratified log-rank test p-value	0.0032	
Progression Free Survival (PFS)[b]		
Number of events, n (%)	454 (73.9%)	393 (64.2%)
Median PFS (95% CI) (months)	4.67 (4.21 to 5.36)	6.90 (6.51 to 7.20)
Stratified hazard ratio (95% CI)	0.758 (0.661 to 0.869)	
Stratified log-rank test p-value	0.00007	
Overall Response Rate (CR+PR) (95% CI) (%)[c]	11.1 (8.5 to 13.8)	19.8 (16.4 to 23.2)
Stratified Cochran-Mantel-Haenszel test p-value	0.0001	

a Stratified on ECOG performance status (0 versus 1 versus 2) and prior bevacizumab (yes versus no).
b PFS (based on tumour assessment by the IRC): Significance threshold is set to 0.0001
c Overall objective response rate by IRC

Analyses for overall survival by stratification factors showed a consistent treatment effect in favour of patients treated with Zaltrap/FOLFIRI regimen for patients with prior bevacizumab use [hazard ratio (HR): 0.862; (95% CI: 0.676 to 1.1)] as well as in patients without prior bevacizumab use [HR: 0.788 (95% CI: 0.671 to 0.925)]. A consistent treatment effect was also seen in patients with an ECOG performance status 0 and 1. The hazard ratio of overall survival is 0.768 (95% CI: 0.637 to 0.925) for ECOG performance status 0 and 0.869 (95% CI: 0.712 to 1.052) for ECOG performance status 1.

For progression free survival, the HR (95% CI) for patients with prior bevacizumab is 0.661 (95% CI: 0.512 to 0.852) and 0.797 (95% CI: 0.679 to 0.936) for patients without prior bevacizumab. The hazard ratio of progression free survival is 0.761 (95% CI: 0.633 to 0.913) for ECOG performance status 0 and 0.749 (95% CI: 0.607 to 0.923) for ECOG performance status 1.

Subgroup analyses for overall survival and progression free survival according to age (<65years; ≥65 years), gender, prior bevacizumab use, ECOG performance status 0 and 1, presence of liver metastasis only, history of prior hypertension, and number of organs involved, showed a treatment effect favouring the Zaltrap/FOLFIRI regimen over the placebo/FOLFIRI regimen.

In sub-group analysis of overall survival, a benefit consistent with the overall population was observed in patients <65 years old and ≥65 years old who received the Zaltrap/FOLFIRI regimen.

INDICATION

Zaltrap in combination with irinotecan-fluoropyrimidine-based chemotherapy is indicated in adults with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.

[See CLINICAL TRIALS for results of Zaltrap in combination with FOLFIRI. Other combinations have not been evaluated].

CONTRAINDICATIONS

Zaltrap is contraindicated in patients with a known severe hypersensitivity to aflibercept or to any of the excipients listed in the Description section.

Zaltrap is contraindicated for ophthalmic/intravitreal use due to hyperosmotic properties of Zaltrap (see PRECAUTIONS).

For contraindications related to irinotecan, 5-FU, and folinic acid, refer to the current respective Product Information documents.

PRECAUTIONS

Haemorrhage

Patients treated with aflibercept have an increased risk of haemorrhage, including severe and sometimes fatal haemorrhagic events (see ADVERSE EFFECTS).

Patients should be monitored for signs and symptoms of gastrointestinal bleeding and other severe bleeding. Aflibercept should not be administered to patients with severe haemorrhage (see DOSAGE AND ADMINISTRATION).

Gastrointestinal perforation

Gastrointestinal perforation including fatal gastrointestinal perforation has been reported in patients treated with aflibercept (see ADVERSE EFFECTS).

Patients should be monitored for signs and symptoms of gastrointestinal perforation. Aflibercept treatment should be discontinued in patients who experience gastrointestinal perforation (see DOSAGE AND ADMINISTRATION).

Fistula formation

Fistula formation involving gastrointestinal and non-gastrointestinal sites has occurred in patients treated with aflibercept (see ADVERSE EFFECTS).

Aflibercept treatment should be discontinued in patients who develop fistula (see DOSAGE AND ADMINISTRATION).

Hypertension

An increased risk of grade 3-4 hypertension (including hypertension and one case of essential hypertension) has been observed in patients receiving aflibercept/FOLFIRI regimen (see ADVERSE EFFECTS).

Pre-existing hypertension must be adequately controlled before starting aflibercept. If hypertension cannot be adequately controlled, treatment with aflibercept should not be initiated. It is recommended to monitor blood pressure every two weeks or as clinically indicated during treatment with aflibercept. In the event of hypertension, patients should be treated with appropriate anti-hypertensive therapy and blood pressure should be monitored regularly. Aflibercept treatment should be suspended for patients with uncontrolled hypertension. For recurrence of severe hypertension, the treatment should be suspended until controlled and the aflibercept dose should be reduced to 2 mg/kg for subsequent cycles. Aflibercept should be permanently discontinued if hypertensive crisis or hypertensive encephalopathy occurs (see DOSAGE AND ADMINISTRATION).

Hypertension may exacerbate underlying cardiovascular disease. Caution should be exercised when treating patients with history of clinically significant cardiovascular disease such as coronary artery disease or congestive heart failure with aflibercept. Patients with heart failure New York Heart Association (NYHA) class III or IV should not be treated with aflibercept.

Arterial thromboembolic events

Arterial thromboembolic events (including transient ischaemic attack, cerebrovascular accident, angina pectoris, intracardiac thrombus, myocardial infarction, arterial embolism, and ischaemic colitis) have been observed in patients who have received aflibercept (see ADVERSE EFFECTS).

Aflibercept treatment should be discontinued in patients who experience an arterial thromboembolic event (see DOSAGE AND ADMINISTRATION).

Venous thromboembolic events

Venous thromboembolic events including deep vein thrombosis (DVT) and pulmonary embolism have been reported in patients treated with aflibercept (see ADVERSE EFFECTS).

Aflibercept should be discontinued in patients with life threatening (Grade 4) thromboembolic events (including pulmonary embolism) (see DOSAGE AND ADMINISTRATION). Patients with Grade 3 DVT should be treated with anticoagulation as clinically indicated, and aflibercept therapy should be continued. In the event of recurrence, despite appropriate anticoagulation, aflibercept treatment should be discontinued. Patients with thromboembolic events of Grade 3 or lower need to be closely monitored.

Proteinuria

Severe proteinuria, nephrotic syndrome, and thrombotic microangiopathy have been observed in patients treated with aflibercept (see ADVERSE EFFECTS).

Proteinuria should be monitored by urine dipstick analysis and urinary protein creatinine ratio (UPCR) for the development or worsening of proteinuria during aflibercept treatment. Patients with a UPCR >1 should undergo a 24-hour urine collection.

Aflibercept administration should be suspended when proteinuria is ≥2 grams/24 hours and restarted when proteinuria is <2 grams/24 hours. If there is a recurrence, the administration should be suspended until <2 grams/24 hours and then the dose reduced to 2 mg/kg. Aflibercept treatment should be discontinued in patients who develop nephrotic syndrome or thrombotic microangiopathy (TMA) (see DOSAGE AND ADMINISTRATION).

Neutropenia and neutropenic complications

A higher incidence of neutropenic complications (febrile neutropenia and neutropenic infection) was reported with the aflibercept/FOLFIRI regimen (see ADVERSE EFFECTS).

Monitoring of complete blood count with differential count is recommended at baseline and prior to initiation of each cycle of aflibercept. Administration of aflibercept/FOLFIRI should be delayed until neutrophil count is ≥1.5 x 10^9/L (see DOSAGE AND ADMINISTRATION). Therapeutic use of Granulocyte-colony stimulating factor at first occurrence of grade ≥3 neutropenia and secondary prophylaxis may be considered in patients who may be at increased risk for neutropenic complications.

Diarrhoea and dehydration

There was a higher incidence of severe diarrhoea with aflibercept/FOLFIRI regimen (see ADVERSE EFFECTS).

Dose modification of FOLFIRI regimen (see DOSAGE AND ADMINISTRATION), institute anti-diarrhoeal medicinal products and rehydration as needed.

Hypersensitivity reactions

In the pivotal study of metastatic colorectal cancer patients, severe hypersensitivity reactions have been reported in patients treated with aflibercept/FOLFIRI regimen (see ADVERSE EFFECTS).

In the event of a severe hypersensitivity reaction (including bronchospasm, dyspnoea, angioedema and anaphylaxis), aflibercept should be discontinued and appropriate medical measures should be administered (see DOSAGE AND ADMINISTRATION and CONTRAINDICATIONS).

In the event of a mild to moderate hypersensitivity reaction (including flushing, rash, urticaria and pruritis), aflibercept should be temporarily suspended until the reaction is resolved. Treatment with corticosteroids and/or antihistamines can be initiated as clinically indicated. Pre-treatment with corticosteroids and/or antihistamines may be considered in subsequent cycles (see DOSAGE AND ADMINISTRATION). Caution should be used when re-treating patients with prior hypersensitivity reactions as recurrent hypersensitivity reactions have been observed in some patients despite prophylaxis, including with corticosteroids.

Compromised wound healing

Aflibercept impairs wound healing in animal models. Aflibercept administration resulted in a delay in wound healing in rabbits. In full-thickness excisional and incisional skin wound models, aflibercept administration reduced fibrous response, neovascularisation, epidermal hyperplasia/re-epithelialisation, and tensile strength.

Treatment with aflibercept is associated with a potential for compromised wound healing (wound dehiscence, anastomotic leakage) (see ADVERSE EFFECTS).

Aflibercept should be suspended for at least 4 weeks prior to elective surgery.

It is recommended that aflibercept not be initiated for at least 4 weeks following major surgery and not until the surgical wound is fully healed. For minor surgery such as central venous access port placement, biopsy, and tooth extraction, aflibercept may be initiated/restarted once the surgical wound is fully healed. Aflibercept should be discontinued in patients with compromised wound healing requiring medical intervention (see DOSAGE AND ADMINISTRATION).

Reversible posterior leukoencephalopathy syndrome (RPLS)

RPLS has not been reported in the pivotal phase III study of metastatic colorectal patients. RPLS was reported in patients treated with aflibercept as monotherapy and in combination with other chemotherapies (see ADVERSE EFFECTS).

RPLS may present with altered mental status, seizure, nausea, vomiting, headache, or visual disturbances. The diagnosis of RPLS is confirmed by brain Magnetic Resonance Imaging.

Aflibercept should be discontinued in patients that develop RPLS (see DOSAGE AND ADMINISTRATION).

Off label intravitreal use

Zaltrap is a hyperosmotic solution, which is not formulated for compatibility with the intraocular environment. Zaltrap must not be administered as an intravitreal injection (see CONTRAINDICATIONS).

EFFECTS ON FERTILITY

Male and female fertility are likely to be compromised during treatment with aflibercept based on studies in monkeys. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 30mg/kg every one to two weeks. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility (considered consequential of male fertility) were observed at all dose levels. Systemic exposure to free aflibercept in monkeys at the lowest observed effect level was similar to the exposure observed in humans after an IV dose of 4mg/kg. All changes were reversible.

Women of childbearing potential should be advised to avoid becoming pregnant while on aflibercept and should be apprised of the potential hazard to the foetus. Women of childbearing potential and fertile males should use effective contraception during and up to a minimum of 6 months after the last dose of treatment.

USE IN PREGNANCY (CATEGORY D)

There are no data from the use of aflibercept in pregnant women. Studies in animals have shown reproductive toxicity including external, visceral, and skeletal foetal malformations.

Aflibercept produced malformations and other foetal abnormalities in pregnant rabbits with intravenous administration at 3 to 60mg/kg once every 3 days during the period of organogenesis. A No Observed Effect Level (NOEL) for adverse effects on embryofoetal development was not established. Systemic exposure to free aflibercept at the lowest observed effect level was less than the exposure observed in humans after an IV dose of 4mg/kg.

As angiogenesis is critical to foetal development, the inhibition of angiogenesis following administration of aflibercept may result in adverse effects on pregnancy. Aflibercept should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. If this

medicinal product is used during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be apprised of the potential hazard to the foetus. Aflibercept is not recommended during pregnancy and in women of childbearing potential not using contraception. Women of childbearing potential should use effective contraception during and up to a minimum of 6 months after the last dose of treatment.

USE IN LACTATION

No studies have been conducted to assess the impact of aflibercept on milk production, its presence in breast milk or its effects on the breast-fed child.

It is not known whether aflibercept 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 aflibercept, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PAEDIATRIC USE

Safety and effectiveness in paediatric patients have not been established.

USE IN THE ELDERLY

No dose adjustments of aflibercept are required for the elderly(see DOSAGE AND ADMINISTRATION). Elderly patients ≥65 years had an increased risk of diarrhoea, dizziness, asthenia, weight loss and dehydration. Careful monitoring is recommended in order to rapidly detect and treat signs and symptoms of diarrhoea and dehydration and to minimize potential risk (see ADVERSE EVENTS).

GENOTOXICITY

No studies have been conducted to evaluate mutagenic or clastogenic potential of aflibercept. As a large protein molecule, aflibercept is not expected to interact directly with DNA or other chromosomal material.

CARCINOGENICITY

No studies have been conducted to evaluate carcinogenicity or mutagenicity of aflibercept.

EFFECT ON LABORATORY TESTS

Effects on laboratory testing were not evaluated in studies.

INTERACTIONS WITH OTHER MEDICINES

No interaction studies have been performed.

Free and bound aflibercept concentrations measured in combination studies were comparable to those measured in the single agent study, suggesting that these combinations (including oxaliplatin, cisplatin, 5 FU, irinotecan, docetaxel, pemetrexed, gemcitabine and erlotinib) have no impact on the pharmacokinetics of aflibercept.

Based on phase I combination studies, and compared to historical or published data, aflibercept had no impact on the pharmacokinetics of irinotecan, 5-FU, oxaliplatin, cisplatin, docetaxel, pemetrexed, gemcitabine, and erlotinib.

ADVERSE EFFECTS

Summary of the safety profile

The safety of aflibercept in combination with FOLFIRI was evaluated in 611 previously treated patients with metastatic colorectal cancer who were treated with aflibercept 4 mg/kg every two weeks (one cycle) versus 605 patients who were treated with placebo/FOLFIRI in a phase III study. Patients received a median number of 9 cycles of aflibercept/FOLFIRI regimen.

The most common adverse reactions (all grades, ≥20% incidence) reported at least 2% greater incidence for the aflibercept/FOLFIRI regimen as compared to the placebo/FOLFIRI regimen in order of decreasing frequency were leucopenia, diarrhoea, 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 2).

The most common reported grades 3-4 reactions (≥5%) reported at least 2% greater incidence for the aflibercept/FOLFIRI regimen as compared to the placebo/FOLFIRI regimen in order of decreasing frequency, were neutropenia, diarrhoea, hypertension, leucopenia, stomatitis, fatigue, proteinuria, and asthenia (see Table 2).

Overall treatment discontinuation due to adverse reactions (all grades) was reported in 26.8% of patients treated with aflibercept/FOLFIRI regimen. The most frequent adverse reactions leading to permanent discontinuation in ≥1% of patients treated with aflibercept/FOLFIRI regimen were

asthenia/fatigue, infections, diarrhoea, dehydration, hypertension, stomatitis, venous thromboembolic events, neutropenia, and proteinuria.

Aflibercept was dose-modified (reductions and/or omissions) in 16.7% of patients. Cycle delays >7 days occurred in 59.7% of patients treated with the aflibercept/FOLFIRI regimen.

Deaths due to causes other than disease progression occurring within 30 days of last administration of study treatment were reported in 16/611 patients (2.6%) treated with the aflibercept/FOLFIRI regimen. The causes for these deaths in patients receiving the aflibercept/FOLFIRI regimen were infection (including neutropenic sepsis) in 4 patients, dehydration in 2 patients, hypovolemia in 1 patient, metabolic encephalopathy in 1 patient, respiratory events (acute respiratory failure, aspiration pneumonia, and pulmonary embolism) in 3 patients, gastrointestinal disorders (duodenal ulcer haemorrhage, gastrointestinal inflammation, and large intestinal obstruction) in 3 patients, and death of unknown cause in 2 patients.

Tabulated summary of adverse reactions

Table 2 presents the adverse reactions and laboratory abnormalities (all grades) reported as a higher incidence (≥2%) in patients treated with aflibercept/FOLFIRI regimen as compared to patients treated with placebo/FOLFIRI regimen from the metastatic colorectal cancer study.

Table 2 - Adverse reactions and laboratory abnormalities (all grades) reported as a higher incidence (≥2%) in patients treated with aflibercept/FOLFIRI regimen as compared to patients treated with placebo/FOLFIRI regimen from the metastatic colorectal cancer study

	Placebo/ FOLFIRI (N=605)		aflibercept/ FOLFIRI (N=611)	
Primary System Organ Class Preferred Term n (%)	All grades	Grades 3-4	All grades	Grades 3-4
Infections and infestations				
Urinary Tract Infection	37 (6.1%)	5 (0.8%)	56 (9.2%)	5 (0.8%)
Nasopharyngitis	15 (2.5%)	0	28 (4.6%)	0
Blood and lymphatic system disorders				
Leukopenia*	432 (72.4%)	73 (12.2%)	472 (78.3%)	94 (15.6%)
Neutropenia*	336 (56.3%)	176 (29.5%)	409 (67.8%)	221 (36.7%)
Thrombocytopenia*	202 (33.8%)	10 (1.7%)	286 (47.4%)	20 (3.3%)
Febrile neutropenia	10 (1.7%)	10 (1.7%)	26 (4.3%)	26 (4.3%)
Metabolism and nutrition disorders				
Decreased Appetite	144 (23.8%)	11 (1.8%)	195 (31.9%)	21 (3.4%)
Dehydration	18 (3.0%)	8 (1.3%)	55 (9.0%)	26 (4.3%)
Nervous system disorders				
Headache	53 (8.8%)	2 (0.3%)	136 (22.3%)	10 (1.6%)
Vascular disorders				
Hypertension	65 (10.7%)	9 (1.5%)	252 (41.2%)	117 (19.1%)
Respiratory, thoracic and mediastinal disorders				
Epistaxis	45 (7.4%)	0	169 (27.7%)	1 (0.2%)
Dysphonia	20 (3.3%)	0	155 (25.4%)	3 (0.5%)
Dyspnoea	52 (8.6%)	5 (0.8%)	72 (11.8%)	5 (0.8%)
Oropharyngeal Pain	19 (3.1%)	0	46 (7.5%)	1 (0.2%)
Rhinorrhoea	11 (1.8%)	0	38 (6.2%)	0
Gastrointestinal disorders				
Diarrhoea	342 (56.5%)	47 (7.8%)	423 (69.2%)	118 (19.3%)
Stomatitis	199 (32.9%)	28 (4.6%)	306 (50.1%)	78 (12.8%)

	Placebo/ FOLFIRI (N=605)		aflibercept/ FOLFIRI (N=611)	
Primary System Organ Class Preferred Term n (%)	All grades	Grades 3-4	All grades	Grades 3-4
Abdominal Pain	143 (23.6%)	14 (2.3%)	164 (26.8%)	27 (4.4%)
Abdominal Pain Upper	48 (7.9%)	6 (1.0%)	66 (10.8%)	7 (1.1%)
Haemorrhoids	13 (2.1%)	0	35 (5.7%)	0
Rectal Haemorrhage	15 (2.5%)	3 (0.5%)	32 (5.2%)	4 (0.7%)
Proctalgia	11 (1.8%)	2 (0.3%)	32 (5.2%)	2 (0.3%)
Aphthous stomatitis	14 (2.3%)	0	30 (4.9%)	4 (0.7%)
Toothache	5 (0.8%)	0	19 (3.1%)	0
Skin and subcutaneous tissue disorders				
Palmar-Plantar Erythrodysesthesia Syndrome	26 (4.3%)	3 (0.5%)	67 (11.0%)	17 (2.8%)
Skin Hyperpigmentation	17 (2.8%)	0	50 (8.2%)	0
Renal and urinary disorders				
Proteinuria**	246 (40.7%)	7 (1.2%)	380 (62.2%)	48 (7.9%)
Serum creatinine increased*	108 (18.1%)	3 (0.5%)	136 (22.6%)	0
General disorders and administration site conditions				
Fatigue	236 (39.0%)	47 (7.8%)	292 (47.8%)	77 (12.6%)
Asthenia	80 (13.2%)	18 (3.0%)	112 (18.3%)	31 (5.1%)
Investigations				
AST increased*	296 (50.2%)	10 (1.7%)	339 (57.5%)	18 (3.1%)
ALT increased*	221 (37.1%)	13 (2.2%)	284 (47.3%)	16 (2.7%)
Weight Decreased	87 (14.4%)	5 (0.8%)	195 (31.9%)	16 (2.6%)

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

* Based on laboratory values (percentages done on patients with laboratory assessments)

** Compilation of clinical and laboratory data

Adverse reactions and laboratory abnormalities having ≥2% greater incidence (all grades) in patients treated with aflibercept/FOLFIRI regimen compared to patients treated with placebo/ aflibercept regimen, are listed in Table 3 according to MedDRA system organ class and frequency categories. Within each frequency grouping in a particular system organ class, adverse reactions are presented in order of decreasing seriousness. Intensity of the adverse reactions is graded according to NCI CTC version 3.0 (grade ≥3 = G≥3). Frequencies are based on all grades and defined as: very common (≥1/10), common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100);

rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 3 - Adverse reactions and laboratory abnormalities reported at a higher incidence (≥2%) (all grades) in patients treated with aflibercept/FOLFIRI regimen from the metastatic colorectal cancer study according to MedDRA system organ class and frequency categories

System Organ Class	Adverse Reaction			
Frequency Category		All grades n (%)		Grades 3-4 n (%)
Infections and infestations				
Common	Urinary tract infection	56 (9.2%)		
	Nasopharyngitis	28 (4.6%)		
Uncommon			Urinary tract infection	5 (0.8%)
Blood and lymphatic system disorders				
Very common	Leucopenia*	472 (78.3%)	Leucopenia*	94 (15.6%)
	Neutropenia*	409 (67.8%)	Neutropenia*	221 (36.7%)
	Thrombocytopenia*	286 (47.4%)		
Common	Febrile neutropenia	26 (4.3%)	Febrile neutropenia	26 (4.3%)
			Thrombocytopenia*	20 (3.3%)
Metabolism and nutrition disorders				
Very common	Decreased appetite	195 (31.9%)		
Common	Dehydration	55 (9.0%)	Dehydration	26 (4.3%)
			Decreased appetite	21 (3.4%)
Nervous system disorders				
Very common	Headache	136 (22.3%)		
Common			Headache	10 (1.6%)
Vascular disorders				
Very common	Hypertension	252 (41.2%)	Hypertension	117 (19.1%)
Respiratory, thoracic and mediastinal disorders				

System Organ Class	Adverse Reaction			
Frequency Category		All grades n (%)		Grades 3-4 n (%)
Very common	Dyspnoea	72 (11.8%)		
	Epistaxis	169 (27.7%)		
	Dysphonia	155 (25.4%)		
Common	Oropharyngeal pain	46 (7.5%)		
	Rhinorrhoea	38 (6.2%)		
Uncommon			Dyspnoea	5 (0.8%)
			Epistaxis	1 (0.2%)
			Dysphonia	3 (0.5%)
			Oropharyngeal pain	1 (0.2%)
Gstrointestinal disorders				
Very common	Diarrhoea	423 (69.2%)	Diarrhoea	118 (19.3%)
	Stomatitis	306 (50.1%)	Stomatitis	78 (12.8%)
	Abdominal pain	164 (26.8%)		
	Abdominal pain upper	66 (10.8%)		
Common	Rectal haemorrhage	32 (5.2%)	Abdominal pain	27 (4.4%)
	Aphthous stomatitis	30 (4.9%)	Abdominal pain upper	7 (1.1%)
	Haemorrhoids	35 (5.7%)		
	Proctalgia	32 (5.2%)		
	Toothache	19 (3.1%)		
Uncommon			Rectal haemorrhage	4 (0.7%)
			Aphthous stomatitis	4 (0.7%)
			Proctalgia	2 (0.3%)
Skin and subcutaneous tissue disorders				
Very common	Palmar-Plantar Erythrodysesthesia syndrome	67 (11.0%)		
Common	Skin hyperpigmentation	50 (8.2%)	Palmar-Plantar Erythrodysesthesia syndrome	17 (2.8%)
Renal and urinary disorders				

System Organ Class	Adverse Reaction			
Frequency Category		All grades n (%)		Grades 3-4 n (%)
Very common	Proteinuria**	380 (62.2%)		
	Serum creatinine increased	136 (22.6%)		
Common			Proteinuria**	48 (7.9%)
General disorders and administration site conditions				
Very common	Fatigue	292 (47.8%)	Fatigue	77 (12.6%)
	Asthenia	112 (18.3%)		
Common			Asthenia	31 (5.1%)
Investigations				
Very common	AST increased*	339 (57.5%)		
	ALT increased*	284 (47.3%)		
	Weight decreased	195 (31.9%)		
Common			AST increased*	18 (3.1%)
			ALT increased*	16 (2.7%)
			Weight decreased	16 (2.6%)

Note: Adverse reactions are reported using MedDRA version MEDDRA13.1 and graded using NCI CTC version 3.0
* Based on laboratory values (percentages done on patients with laboratory assessments)
** Compilation of clinical and laboratory data
AST = aspartate transaminase
AST= alanine transaminase

In the pivotal metastatic colorectal cancer study (VELOUR), adverse events and laboratory abnormalities occurring in ≥20% of patients that were comparable between groups (did not exceed ≥2% higher incidence for the aflibercept/FOLFIRI regimen) were anaemia, nausea, vomiting, constipation, alopecia, alkaline phosphatase increased, and hyperbilirubinaemia.

Description of selected adverse reactions

Haemorrhage

Patients treated with aflibercept have an increased risk of haemorrhage, including severe and sometimes fatal haemorrhagic events. In the pivotal study of metastatic colorectal cancer patients, episodes of bleeding/haemorrhage (all grades) was reported in 37.8% of patients treated with aflibercept/FOLFIRI regimen compared to 19.0% of patients treated with placebo/FOLFIRI

regimen. The most common reported form of bleeding was minor (grade 1-2) epistaxis occurring in 27.7% of patients treated with aflibercept/FOLFIRI regimen. Grade 3-4 haemorrhage including gastrointestinal haemorrhage, haematuria, and post-procedural haemorrhage was reported in 2.9% of patients receiving aflibercept/FOLFIRI regimen compared with 1.7% of patients receiving placebo/FOLFIRI regimen. In other studies, severe intracranial haemorrhage and pulmonary haemorrhage/haemoptysis including fatal events have occurred in patients receiving aflibercept (see PRECAUTIONS).

Gastrointestinal perforation

Gastrointestinal perforation including fatal gastrointestinal perforation has been reported in patients treated with aflibercept. In the pivotal study of metastatic colorectal cancer patients, gastrointestinal perforation (all grades) was reported in 3 of 611 patients (0.5%) treated with aflibercept/FOLFIRI regimen and 3 of 605 patients (0.5%) treated with placebo/FOLFIRI regimen. Grade 3-4 gastrointestinal perforation events occurred in all 3 patients (0.5%) treated with aflibercept/FOLFIRI regimen and in 2 patients (0.3%) treated with placebo/FOLFIRI regimen. Across three Phase 3 placebo-controlled clinical studies (colorectal, pancreatic, and lung cancer populations), the incidence of gastrointestinal perforation (all grades) was 0.8% for patients treated with aflibercept and 0.3% for patients treated with placebo. Grade 3-4 gastrointestinal perforation events occurred in 0.8% of patients treated with aflibercept and 0.2% of patients treated with placebo (see PRECAUTIONS).

Fistula formation

Fistula formation involving gastrointestinal and non-gastrointestinal sites has occurred in patients treated with aflibercept. In the pivotal study of metastatic colorectal patients, fistulas (anal, enterovesical, enterocutaneous, colovaginal, intestinal sites) were reported in 9 of 611 patients (1.5%) treated with aflibercept/FOLFIRI regimen and 3 of 605 patients (0.5%) treated with placebo/FOLFIRI regimen. Grade 3 gastrointestinal fistula formation occurred in 2 patients treated with aflibercept (0.3%) and in 1 placebo treated patient (0.2%) (see PRECAUTIONS).

Hypertension

In the pivotal study of metastatic colorectal cancer patients, hypertension (all grades) has been reported in 41.2% of patients treated with aflibercept/FOLFIRI and 10.7% of patients treated with placebo/FOLFIRI. An increased risk of grade 3-4 hypertension (including hypertension and one case of essential hypertension) has been observed in patients receiving aflibercept/ FOLFIRI regimen. Grade 3 hypertension (requiring adjustment in existing anti-hypertensive therapy or treatment with more than one medicinal product) was reported in 1.5% of patients treated with placebo/FOLFIRI regimen and 19.1% of patients treated with aflibercept/FOLFIRI regimen. Grade 4 hypertension (hypertensive crisis) was reported in 1 patient (0.2%) treated with aflibercept/FOLFIRI regimen. Among those patients treated with aflibercept/FOLFIRI regimen

developing grade 3-4 hypertension, 54% had onset during the first two cycles of treatment (see PRECAUTIONS).

Arterial thromboembolic events (ATE)

In the pivotal study of metastatic colorectal cancer patients, ATE (including transient ischemic attack, cerebrovascular accident, angina pectoris, intracardiac thrombus, myocardial infarction, arterial embolism, and ischemic colitis) were reported in 2.6% of patients treated with aflibercept/FOLFIRI regimen and 1.5% of patients treated with placebo/FOLFIRI regimen. Grade 3-4 events occurred in 11 patients (1.8%) treated with aflibercept/FOLFIRI regimen and 3 patients (0.5%) treated with placebo/FOLFIRI regimen (see PRECAUTIONS).

Venous thromboembolism events

Adverse event terms grouped as venous thromboembolic events include deep venous thrombosis and pulmonary embolism. In the pivotal study of metastatic colorectal cancer patients, all grades venous thromboembolic events occurred in 9.3% of patients treated with aflibercept/FOLFIRI regimen and 7.3% of patients treated with placebo/FOLFIRI regimen. Grade 3-4 venous thromboembolic events occurred in 7.9% of patients treated with aflibercept/FOLFIRI regimen and in 6.3% of patients treated with placebo/FOLFIRI regimen. Pulmonary embolism occurred in 4.6% of patients treated with aflibercept/FOLFIRI regimen and 3.5% of patients treated with placebo/FOLFIRI regimen.

Proteinuria

In the pivotal study of metastatic colorectal cancer patients, proteinuria (compiled from clinical and laboratory data) was reported in 62.2% patients treated with aflibercept/FOLFIRI regimen compared to 40.7% patients treated with placebo/FOLFIRI regimen. Grade 3-4 proteinuria occurred in 7.9% of patients treated with aflibercept/FOLFIRI regimen compared to 1.2% of patients treated with placebo/FOLFIRI regimen. Nephrotic syndrome occurred in 2 patients (0.5%) treated with aflibercept/FOLFIRI regimen compared to none of the patients treated with placebo/FOLFIRI regimen. One patient treated with aflibercept/FOLFIRI regimen presenting with proteinuria and hypertension was diagnosed with thrombotic microangiopathy (PRECAUTIONS).

Neutropenia and neutropenic complications

In the pivotal study of metastatic colorectal cancer patients, neutropenia (all grades) has been reported in 67.8% of patients treated with aflibercept/FOLFIRI and 56.3% of patients treated with placebo/FOLFIRI. Grade 3-4 neutropenia was observed in 36.7% of patients treated with aflibercept/FOLFIRI regimen compared to 29.5% patients treated with placebo/FOLFIRI regimen. The most common grade 3-4 neutropenic complication was the occurrence of febrile neutropenia in 4.3% of patients treated with aflibercept/FOLFIRI regimen compared to 1.7% of

patients treated with placebo/FOLFIRI regimen. Grade 3-4 neutropenic infection/sepsis occurred in 1.5% of patients treated with aflibercept/FOLFIRI regimen and 1.2% of patients treated with placebo/FOLFIRI regimen (see PRECAUTIONS).

Infections

Infections occurred at a higher frequency in patients receiving aflibercept/FOLFIRI regimen (46.2%, all grades; 12.3%, grade 3-4) than in patients receiving placebo/FOLFIRI regimen (32.7%, all grades; 6.9%, grade 3-4), including urinary tract infection, nasopharyngitis, upper respiratory tract infection, pneumonia, catheter site infection, and tooth infection.

Diarrhoea and dehydration

In the pivotal study of metastatic colorectal cancer patients, diarrhoea (all grades) has been observed in 69.2% of patients treated with aflibercept/FOLFIRI and 56.5% of patients treated with placebo/FOLFIRI. Dehydration (all grades) has been observed in 9.0% of patients treated with aflibercept/FOLFIRI and 3.0% of patients treated with placebo/FOLFIRI. Grade 3-4 diarrhoea was reported in 19.3% of patients treated with aflibercept/FOLFIRI regimen compared to 7.8% of patients treated with placebo/FOLFIRI regimen. Grade 3-4 dehydration was reported in 4.3% of patients treated with aflibercept/FOLFIRI regimen compared to 1.3% of patients treated with placebo/FOLFIRI regimen (see PRECAUTIONS).

Hypersensitivity reactions

In the pivotal study of metastatic colorectal cancer patients, severe hypersensitivity reactions have been reported in 0.3% of patients treated with aflibercept/FOLFIRI regimen and 0.5% of patients treated with placebo/FOLFIRI regimen (see PRECAUTIONS).

Compromised wound healing

Treatment with aflibercept is associated with potential for compromised wound healing (wound dehiscence, anastomotic leakage). In the pivotal study for metastatic colorectal cancer, compromised wound healing was reported in 3 patients (0.5%) treated with aflibercept/FOLFIRI regimen and 5 patients (0.8%) treated with placebo/FOLFIRI regimen. Grade 3 compromised wound healing was reported in 2 patients (0.3%) treated with aflibercept/FOLFIRI regimen and in none of the patients treated with placebo/FOLFIRI regimen (see PRECAUTIONS).

Reversible posterior leukoencephalopathy syndrome (RPLS)

RPLS has not been reported in the pivotal Phase III study of metastatic colorectal cancer patients. RPLS was reported in patients treated with monotherapy aflibercept (0.5%) and in combination with other chemotherapies (see PRECAUTIONS).

Other special populations

Elderly

Of the 611 patients treated with aflibercept/FOLFIRI regimen in the pivotal study of metastatic CRC patients, 172 (28.2%) were age ≥65 years and <75 years and 33 (5.4%) were age ≥75 years. Elderly patients (≥65 years of age) may be more likely to experience adverse reactions. The incidence of diarrhoea, dizziness, asthenia, weight decrease, and dehydration was ≥5% higher in elderly patients compared to younger patients. Elderly patients should be closely monitored for the development of diarrhoea and potential dehydration (see PRECAUTIONS).

Paediatric population

The safety in paediatric patients has not been established.

Renal impairment

In patients receiving aflibercept, the adverse reactions in patients with mild renal impairment at baseline in aggregate Phase III studies (N=352) were comparable with those of patients without renal impairment (N=642). A limited number of patients having moderate/severe renal impairment at baseline (N=49) were treated with aflibercept. In these patients, non-renal events were generally comparable between patients with renal impairment and those without renal impairment, except a >10% higher incidence in dehydration (all grades) was noted.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with aflibercept.

Overall across all clinical oncology studies, similar incidence of low titer anti-drug antibody (ADA) responses (post baseline) in the ADA assay were observed in both patients treated with placebo and aflibercept (3.3% and 3.8%, respectively). High titer antibody responses to aflibercept were not detected in any patients. Seventeen (17) patients treated with aflibercept (1.6 %) and two (2) placebo treated patients (0.2%) were also positive in the neutralising antibody assay. In the pivotal study of metastatic colorectal cancer patients (VELOUR), positive responses in the ADA assay were observed at higher levels in patients treated with placebo/FOLFIRI regimen [18/526 (3.4%)] than with aflibercept/FOLFIRI regimen [8/521 (1.5%)]. Positive results in the neutralising antibody assay in the MCRC pivotal study were also higher in patients treated with placebo/FOLFIRI regimen [2/526 (0.38%)] than with aflibercept/FOLFIRI regimen [1/521 (0.19%)]. There was no observed impact on the pharmacokinetic profile of aflibercept in patients who were positive in the immunogenicity assays.

Given the similar ADA assay results in patients treated with placebo or aflibercept, the actual incidence of immunogenicity with aflibercept based on these assays is likely to be overestimated.

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 aflibercept with the incidence of antibodies to other products may be misleading.

DOSAGE AND ADMINISTRATION

Dosage

The recommended dose of Zaltrap, administered as an intravenous infusion over 1 hour, is 4 mg/kg of body weight, followed by the FOLFIRI regimen.

The FOLFIRI regimen used in the VELOUR study was irinotecan 180 mg/m^2 intravenous infusion over 90 minutes and folinic acid (dl racemic) 400 mg/m² intravenous infusion over 2 hours at the same time on day 1 using a Y line, followed by 5-fluorouracil (5-FU) 400 mg/m² intravenous bolus, followed by 5 FU 2400 mg/m² continuous intravenous infusion over 46 hours.

The treatment cycles are repeated every 2 weeks.

Zaltrap treatment should be continued until disease progression or unacceptable toxicity occurs.

Dose modification/Discontinuations/Treatment delay recommendations

Discontinue Zaltrap for (see PRECAUTIONS):

- Severe haemorrhage
- Gastrointestinal perforation
- Fistula formation
- Hypertensive crisis or hypertensive encephalopathy
- Arterial thromboembolic events
- Grade 4 venous thromboembolic events (including pulmonary embolism)
- Nephrotic syndrome or thrombotic microangiopathy
- Severe hypersensitivity reactions (including bronchospasm, dyspnea, angioedema, and anaphylaxis)

- Compromised wound healing requiring medical intervention
- Reversible posterior leukoencephalopathy syndrome

Temporarily suspend Zaltrap at least 4 weeks prior to elective surgery (see PRECAUTIONS).

Zaltrap/FOLFIRI Treatment delay	
Neutropenia or thrombocytopenia (see PRECAUTIONS and ADVERSE EFFECTS)	Administration of Zaltrap/FOLFIRI should be delayed until neutrophil count is ³ 1.5 x 10^9/L or platelet count is ³ 75 x 10^9/L.
Mild to moderate hypersensitivity reaction (including flushing, rash, urticaria, and pruritis) (see PRECAUTIONS)	Temporarily suspend the treatment until the reaction resolves. Treat with corticosteroids and/or antihistamines as clinically indicated. Pre-treatment with corticosteroids and/or antihistamines may be considered in subsequent cycles.
Severe hypersensitivity reactions (including bronchospasm, dyspnoea, angioedema, and anaphylaxis) (see CONTRAINDICATIONS and PRECAUTIONS)	Discontinue Zaltrap and administer appropriate medical therapy.
Zaltrap Treatment delay and dose modification	
Hypertension (see PRECAUTIONS)	Temporarily suspend Zaltrap until hypertension is controlled. For recurrence of severe hypertension, suspend until controlled and reduce dose to 2 mg/kg for subsequent cycles.
Proteinuria (see PRECAUTIONS)	Suspend Zaltrap when proteinuria ≥2 grams per 24 hours and resume when proteinuria <2 grams per 24 hours. If recurrence, suspend until <2 grams per 24 hours and then reduce dose to 2 mg/kg.
FOLFIRI Dose modification when used in combination with Zaltrap	
Severe stomatitis and Palmar-Plantar Erythrodysesthesia syndrome	Reduce 5-FU bolus and infusion dose by 20%.
Severe diarrhoea	Reduce irinotecan dose by 15-20%. If severe diarrhoea recurs on subsequent cycle, additionally reduce 5-FU bolus and infusion dose by 20%. If severe diarrhoea persists with both dose reductions, discontinue FOLFIRI. Treat with anti-diarrhoeal medications and rehydration as needed.

Febrile neutropenia or neutropenic sepsis	Reduce irinotecan dose by 15-20% in subsequent cycles. If recurrence, additionally reduce 5-FU bolus and infusion dose by 20% in subsequent cycles. The use of G-CSF may be considered.

For additional toxicities related to irinotecan, 5-FU, and folinic acid refer to the current respective Product Information documents.

Special populations

Paediatric population

Safety and effectiveness in paediatric patients have not been established.

Elderly

No dose adjustment of Zaltrap is required for the elderly.

Hepatic impairment

There have been no formal studies with Zaltrap in patients with hepatic impairment (see PHARMACOKINETICS).

Renal impairment

There have been no formal studies with Zaltrap in patients with renal impairment (see PHARMACOKINETICS).

Administration

Zaltrap is for intravenous infusion use only. The Zaltrap concentrate must be diluted before administration.

Zaltrap is a sterile, preservative-free and non-pyrogenic solution, therefore the solution for infusion should be prepared by a healthcare professional using safe-handling procedures and aseptic technique.

As with any other medicinal product, caution should be exercised when handling Zaltrap, taking into account the use of containment devices, personal protective equipment (e.g. gloves), and preparation procedures.

Preparation of the infusion solution:

1) Inspect visually the Zaltrap vial prior to use. The concentrate solution must be clear without particles.

2) Based on the required dose for the patient, withdraw the necessary volume of Zaltrap concentrate (25mg/mL) from the vial. More than 1 vial could be needed for the preparation of the infusion solution.

3) Dilute it to the required administration volume with sodium chloride 9 mg/mL (0.9%) solution or 5% glucose solution for infusion. The concentration of the final Zaltrap solution for intravenous infusion should be kept within the range of 0.6 - 8 mg/mL of aflibercept. Infusion bags made of polyvinyl chloride (PVC) containing bis(2-ethylhexyl) phthalate (DEHP) or polyolefin (PVC-free DEHP-free) should be used.

Product is for single use in one patient only. Do not re-enter the vial after the initial puncture. Any unused concentrate should be discarded.

As with all parenteral medicinal products, Zaltrap diluted solution should be inspected visually for particulate matter and discoloration prior to administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Administration of the infusion solution:

Zaltrap should be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

As with all parenteral medicinal products, Zaltrap diluted solution should be inspected visually for particulate matter and discoloration prior to administration.

Zaltrap is for intravenous infusion use only. Due to hyperosmolality (1,000 mOsmol/kg) of the Zaltrap concentrate, undiluted Zaltrap concentrate must not be administered as an intravenous push or bolus. Zaltrap must not be administered as an intravitreal injection.

Diluted Zaltrap intravenous infusions should be administered using a 0.2 micron in-line polyethersulfone filter. Do not use filters made of polyvinylidene fluoride (PVDF) or nylon.

Diluted solutions of Zaltrap should be administered using infusion sets made of one of the following materials:

- polyvinyl chloride (PVC) containing bis(2-ethylhexyl) phthalate (DEHP)
- DEHP free PVC containing trioctyl-trimellitate (TOTM)

- polypropylene
- polyethylene lined PVC
- polyurethane

Diluted Zaltrap infusion solution should be used immediately. However, in-use storage time can be longer under specific conditions mentioned in the Presentation and Storage section.

Any unused product or waste material should be disposed of in accordance with local requirements.

OVERDOSAGE

There have been no cases of overdose reported with Zaltrap. There is no information on the safety of aflibercept given at doses exceeding 7 mg/kg every 2 weeks or 9 mg/kg every 3 weeks. The most commonly observed adverse events at these doses were similar to those observed at the therapeutic dose.

There is no specific antidote to Zaltrap overdose. Cases of overdose should be managed by appropriate supportive measures particularly in regards to monitoring and treatment of hypertension and proteinuria. The patient should remain under close medical supervision to monitor any adverse reactions (see ADVERSE EFFECTS).

For information on the management of overdose, contact the Poison Information Centre on 131126.

PRESENTATION AND STORAGE CONDITIONS

Zaltrap concentrated vial contains 25mg/mL of aflibercept.

100mg/4mL presentation

Each 5mL vial contains 100mg of aflibercept in 4mL. Supplied as:

1 vial per carton and

3 vials per carton *

200mg/8mL presentation

Each 10mL vial contains 200mg of aflibercept in 8mL. Supplied as:

1 vial per carton

Vials should be stored in their original, unopened container. Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C and for 8 hours at 25°C.

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours or not more than 8 hours at room temperature.

* Not marketed

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE ARTG

02 April 2013