CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Summary Review

Date	August 1, 2012
From	Richard Pazdur, MD
Subject	Office Director Summary Review
BLA #	STN BL 125418/0
Applicant Name	sanofi-aventis U.S. LLC
Date of Submission	February 3, 2012
PDUFA Goal Date	August 4, 2012
Proprietary Name / Established (USAN) Name	Zaltrap ziv-aflibercept Injection
Dosage Forms / Strength	solution for injection/supplied in vials containing 100 mg (25 mg/mL) and 200 mg (25 mg/mL)
Proposed Indication(s)	For the treatment of metastatic colorectal cancer, in combination with the chemotherapy regimen 5-fluorouracil, irinotecan, and leucovorin (FOLFIRI)
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director	Patricia Keegan
CDTL Review	Steven Lemery
Reg. Project Manager Review	Melanie Pierce
Medical Officer Review	Sandra Casak
Statistical Review	Jenny Zhang/Kun He
Pharmacology Toxicology Review	Alexander Putman/Whitney Helms
OBP Review	Sarah Kennett/Chana Fuchs
Facilities Review	Suvarna Kalavati & Mahesh Ramanadham
Regulatory Project Manager (OBP)	Kimberly Rains
Clinical Pharmacology Review	Ruby Leong/Hong Zhou
Pharmaceutics	Anshu Marathe/Kevin Krudys/ Christine Garnett/
OPDP/DPDP	Carole Broadnax
OSI	Lauren Iacono-Connor/Tejashri Purohit-Sheth
OSE/DMEPA	James Schlick/Todd Bridges

OND=Office of New Drugs
OBP=Office of Biotechnology Products
OPDP= Office of Prescription Drug Promotion
DPDP= Division of Drug Professional Drug Promotion
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations

1. Introduction

This original BLA seeks approval for ZALTRAP (ziv-aflibercept) Injection for the treatment of metastatic colorectal cancer, in combination with 5-fluorouracil, irinotecan, and leucovorin (FOLFIRI) chemotherapy. The mechanism of action of ZALTRAP is postulated to be angiogenesis inhibition, as demonstrated in *in vitro* and *in vivo* models. This product is closely related to the product Eylea (aflibercept, Regeneron), which is approved for the treatment of macular degeneration, however the two products differ in route of administration, product strengths, product formulation, and product purity. In order to minimize medication errors and enhance tracking of post-marketing safety information, FDA required a distinct non-proprietary name for this product, ziv-aflibercept.

Substantial evidence for effectiveness was demonstrated in the results of a single, randomized, placebo-controlled, multicenter, multinational trial (Protocol EFC10262 or VELOUR) enrolling 1226 patients with metastatic colorectal cancer, whose tumors were no longer responsive to oxaliplatin-based chemotherapy. This clinical trial met its primary endpoint, demonstrating a statistically robust and clinically meaningful improvement in overall survival (HR 0.82, p=0.0032), with median survival times of 13.5 and 12.1 months in the ziv-aflibercept/FOLFIRI and FOLFIRI alone arms, respectively. These results are also supported by statistically significant improvements in progression-free survival (PFS) (HR 0.76, p=0.0007), with median PFS times of 6.9 and 4.8 months in the ziv-aflibercept/FOLFIRI and FOLFIRI alone arms, respectively, and a statistically significant increase in overall response rate among patients receiving ziv-aflibercept plus FOLFIRI compared to FOLFIRI alone. These findings were supported by consistent trends favoring the ziv-aflibercept/FOLFIRI arm for subsets based on age, gender, and prior bevacizumab treatment. Although these subsets are underpowered, the benefits of ziv-aflibercept were observed both in subsets of patients who had received and those who had not received prior bevacizumab as part of the first-line treatment for metastatic disease.

Evaluation of the safety of ziv-aflibercept was based primarily on data from three randomized trials (VELOUR, VITAL, and VANILLA) providing safety data on 1333 patients treated with ziv-aflibercept, supported by additional safety data from other Phase 1 and 2 trials for a total database of 2073 patients receiving ziv-aflibercept. The safety profile ziv-aflibercept is similar to that observed with other angiogenesis-inhibiting products.

2. Background

ZALTRAP is the second biologic product for treatment of cancer which mediates its effects through anti-angiogenesis. The other product, Avastin (bevacizumab, Genentech), was first approved in February 2004, for the first-line treatment of colorectal cancer in combination with an infusional 5-fluorouracil-containing combination chemotherapy regimen, based on an improvement in overall survival supported by improvements in progression-free survival.

Indicated Population and Available Therapy

Based on recent data, the National Cancer Institute projects that there will be an estimated 103,170 new cases of colon cancer and 40, 290 new cases of rectal cancer in 2012; NCI also projects that there will be an estimated 51,690 deaths due to colorectal cancer in the United States in 2012. Based on data collected between 2002 through 2008, 20% of colorectal cancers are metastatic at the time of diagnosis, with a 5-year survival rate of 11.9%.

The backbone chemotherapy regimen (FOLFIRI) administered in the VELOUR trial is consistent with the current standard of care in the U.S. for this patient population. Per the NCCN guidelines, acceptable treatment for this patient population includes irinotecan-based chemotherapy, either as a single agent or in combination with fluoropyrimidines or, for frail and elderly patients, single agent capecitabine or a fluoropyrimidines plus leucovorin. In addition, any of these regimens may be combined with bevacizumab. For patients with EGFR-expressing metastatic colorectal cancers without activating mutations in *KRAS*, the addition of cetuximab or panitumumab is also considered acceptable treatment. However, the majority of patients in VELOUR trial (approximately two-

thirds) had not received bevacizumab as a component of first-line treatment for metastatic colorectal cancer. The use of bevacizumab in combination with combination chemotherapy (irinotecan- or oxaliplatin-based) for the initial treatment of metastatic colorectal cancer represents the current standard of care for most patients in the U.S. Bevacizumab labeling was expanded on June 20, 2006, to include a new indication as an adjunct to chemotherapy for the second-line treatment of patients with metastatic colorectal cancer, in combination with an oxaliplatin-containing regimen (FOLFOX4). Patients in this trial (E3200) had received a prior irinotecan-based regimen but not prior bevacizumab for initial treatment of metastatic colorectal cancer. The basis for this approval was demonstration of an improvement in overall survival [HR 0.75 (95% CI: 0.63, 0.89), p=0.001 stratified log rank test] with median survival times of 13.0 months and 10.8 months for patients receiving bevacizumab plus FOLFOX4 and FOLFOX4 alone, respectively.

3. CMC

The chemistry review discipline has provided an overall acceptability of the manufacturing of the drug product and drug substance. (b) (4) A pre-approval inspection for the ziv-aflibercept drug substance production (b) (4) was conducted (b) (4) under BLA 125387 in support of the approval of Eylea. Based on this inspection, the requirement for inspection of this contract manufacturer was waived. Inspections of drug product manufacturing sites were also waived based on based on the compliance history, current GMP status, and previous inspections (b) (4) Stability testing supports an expiry of 36 months when stored at 2-8 °C. There are several requests for post-marketing commitments (PMCs) to further characterize or improve the manufacturing process for ziv-aflibercept. Please see action letter for PMCs.

4. Nonclinical Pharmacology/Toxicology

There are no outstanding pharm/tox issues that preclude approval. Many of the nonclinical studies provided in this BLA were previously submitted to and reviewed under STN BL 125387 in support of marketing approval of Eylea (aflibercept, Regeneron). These included *in vitro* and *in vivo* pharmacodynamic studies assessing binding activity to VEGF, anti-angiogenic and antineoplastic activity and impairment of wound healing in rabbit models. Additionally, the application contained pharmacokinetic studies in two species (rats and cynomolgus monkeys), 3- and 6-month toxicology studies in cynomolgus monkeys, reproductive toxicology studies, and local tolerance studies. No studies were conducted to evaluate carcinogenicity or mutagenicity of aflibercept; this is consistent with FDA's current practice not to require such studies for the intended patient population (metastatic colorectal cancer).

In chronic toxicology trials, weekly/every two weeks intravenous administration of ziv-aflibercept to growing young adult (sexually mature) cynomolgus monkeys resulted in changes in the bone, nasal cavity, kidney, ovary, and adrenal gland. Most of these findings were noted from the lowest dose tested (3 mg/kg/dose) correlating to systemic exposure (AUC) approximately equivalent to those at the human recommended dose. Skeletal and nasal cavity effects were not reversible after a post-dosing recovery period.

Repeated administration of ziv-aflibercept (4 doses administered over 2-3 weeks) resulted in a delay in wound healing in rabbits at dosages ranging from 0.3 mg/kg to 30 mg/kg.

Ziv-aflibercept impaired reproductive function and fertility in monkeys in the 6-month repeat-dose toxicology study, where ziv-aflibercept inhibited ovarian function and follicular development, as evidenced by decreased ovary weight, decreased amount of luteal tissue, decreased number of maturing follicles, atrophy of uterine endometrium and myometrium, vaginal atrophy, abrogation of progesterone peaks and menstrual bleeding. Alterations in sperm morphology and decreased sperm motility were noted in male monkeys. These effects were observed at all doses

tested including the lowest dose tested, 3 mg/kg. Reversibility was observed within 18 weeks after cessation of treatment. Systemic exposure (AUC) with a 3 mg/kg/dose in monkeys was approximately equivalent to AUC in patients at the recommended dose.

5. Clinical Pharmacology

There are no outstanding clinical pharmacology issues that preclude approval. Pharmacokinetic data were provided from 19 trials, including two pharmacodynamic trials in healthy volunteers, trials of both monotherapy and ziv-aflibercept in combination with chemotherapy in patients with various cancers, and a QT/QTc assessment study.

Plasma concentrations of free and VEGF-bound aflibercept were measured using specific enzyme-linked immunosorbent assays (ELISAs). Free aflibercept concentrations appeared to exhibit linear pharmacokinetics in the dose range of 2-9 mg per kg. Following 4 mg per kg every two weeks intravenous administration of ZALTRAP, the elimination half-life of free aflibercept was approximately 6 days (range 4-7 days).

The clinical pharmacology and pharmacometrics reviewers concluded that there was sufficient data to support the proposed dosing regimen. The reviewers concluded that, based on population pharmacokinetic (PK) analyses, there were no clinically meaningful differences in exposure based on age, gender, or race. Based on clinical trial data, no clinically meaningful drug-drug interactions were observed with any of the components of the FOLFIRI or with several other commonly used chemotherapeutic agents; since ziv-aflibercept is a biologic (protein), *in vitro* testing for drug interactions were not performed. There was also no evidence of clinically important prolongation of QT.

The overall incidence of anti-product antibodies (APA) was determined in 15 trials. The incidence of APA was 4.2% in patients receiving intravenous aflibercept (72/1706; of which 19 tested positive at baseline) and 3.5% in placebo-treated patients (41/1156; of which 22 tested positive at baseline). Among patients who tested positive in the APA assay and had sufficient samples for further testing, neutralizing antibodies were detected in 17 of 48 aflibercept-treated patients and in 2 of 40 placebo-treated patients. Among the 17 ziv-aflibercept -treated patients with neutralizing antibodies, mean trough concentrations were lower than in the overall population; however there was insufficient data to determine whether these differences would alter product safety or efficacy.

6. Clinical Microbiology

There are no outstanding product sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

The efficacy data supporting this application is derived from a single, multinational, randomized, placebo-controlled, double-blind trial enrolling 1226 patients with metastatic colorectal cancer. FDA agreed that this single study was acceptable to support an approval provided the treatment effect on overall survival was clinically important, statistically robust, and consistent across relevant subgroups, and supported by other efficacy endpoints (progression-free survival and overall response rate). The results of EFC10262 (the VELOUR trial) met these criteria. The trial was well-conducted with the exception of deviation from Good Clinical Practices and applicable regulations of a single site, however as noted in Dr. Zhang's review, removal of data from this site did not alter the conclusions of the trial.

In the VELOUR trial (Protocol EFC10262), patients were randomized (1:1) to receive ziv-aflibercept in combination with FOLFIRI chemotherapy. Key inclusion criteria were: age ≥ 18 years, histologically- or cytologically-documented adenocarcinoma of the colon or rectum, progression while receiving or following completion of a

maximum of one prior oxaliplatin-containing regimen for the treatment of metastatic disease or relapsed while receiving or within 6 months of completion of an oxaliplatin-containing adjuvant chemotherapy regimen; no prior treatment with irinotecan. Randomization was stratified by ECOG status (0 vs. 1 vs. 2) and prior bevacizumab therapy (yes vs. no) in a permuted block design.

Treatment was administered until progressive disease (PD), unacceptable toxicity, patient refusal, or discontinuation at investigator's discretion.

The co-primary efficacy endpoints were overall survival (OS) and progression-free survival as determined by an independent radiologic review committee. The key secondary endpoint was overall response rate (ORR) as determined by an independent radiologic review committee.

Demographics characteristics were similar between treatment arms. Of the 1226 patients randomized, the median age was 61 years, 59% were men, 87% were White, 7% were Asian, 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 346 patients (28%) received bevacizumab in combination with the prior oxaliplatin-based treatment.

Results

A total of 1226 patients were enrolled in the VELOUR trial between November 19, 2007 and March 16, 2010. The data cut-off date for the final analysis of survival occurred after 863 deaths; median patient follow-up was 22.3 months however 97% of patients were no longer on treatment, primarily due to disease progression.

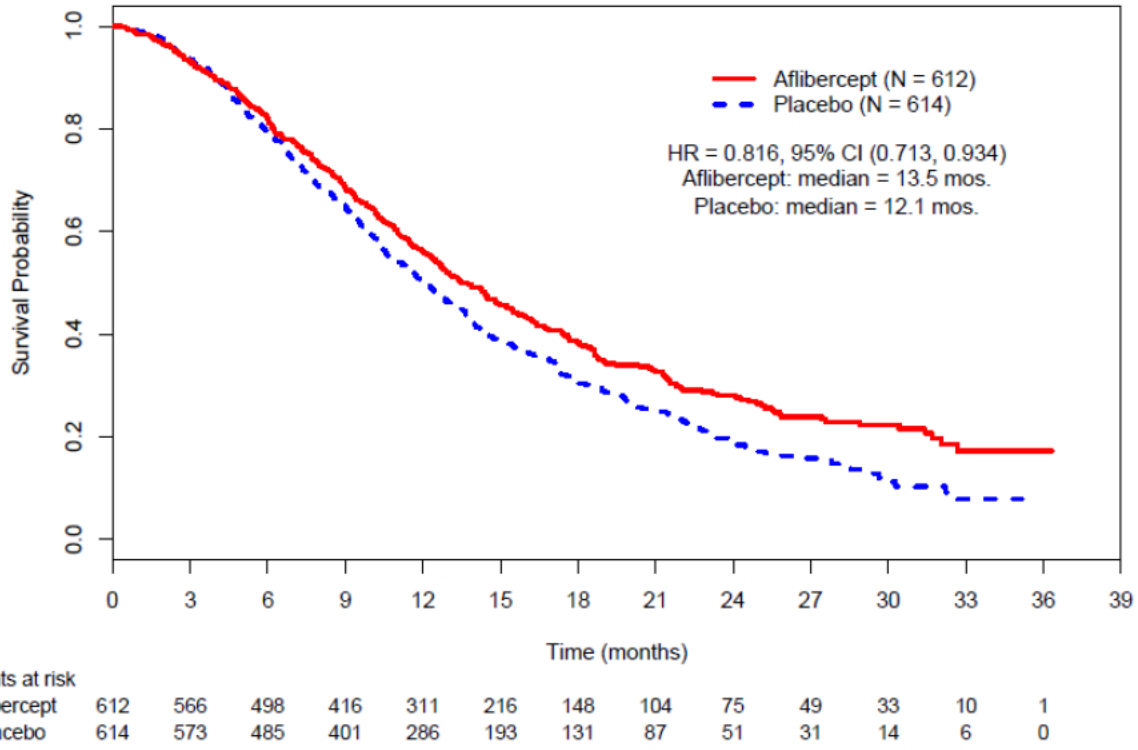
The following demographic information, by study arm and for the trial overall, is abstracted from Dr. Zhang's review (Table 5)

	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)	All (N=1226)
Gender [n(%)]			
Number	614	612	1226
Male	353 (57.5%)	365 (59.6%)	718 (58.6%)
Female	261 (42.5%)	247 (40.4%)	508 (41.4%)
Age (Years)			
Number	614	612	1226
Median	61.0	61.0	61.0
Mean (SD)	60.2 (10.8)	59.5 (10.5)	59.8 (10.7)
Min : Max	19 : 86	21 : 82	19 : 86
Age class [n(%)]			
Number	614	612	1226
<65	376 (61.2%)	407 (66.5%)	783 (63.9%)
≥65 but <75	199 (32.4%)	172 (28.1%)	371 (30.3%)
≥75	39 (6.4%)	33 (5.4%)	72 (5.9%)
Race [n(%)]			
Number	614	612	1226
Caucasian/White	523 (85.2%)	548 (89.5%)	1071 (87.4%)
Black	27 (4.4%)	16 (2.6%)	43 (3.5%)
Asian/Oriental	51 (8.3%)	35 (5.7%)	86 (7.0%)
Other	13 (2.1%)	13 (2.1%)	26 (2.1%)
Region			
Number	614	612	1226
Western Europe	217 (35.3%)	208 (34.0%)	425 (34.7%)
Eastern Europe	136 (22.1%)	161 (26.3%)	297 (24.2%)
North America	75 (12.2%)	63 (10.3%)	138 (11.3%)
South America	56 (9.1%)	62 (10.1%)	118 (9.6%)
Other countries	130 (21.2%)	118 (19.3%)	248 (20.2%)

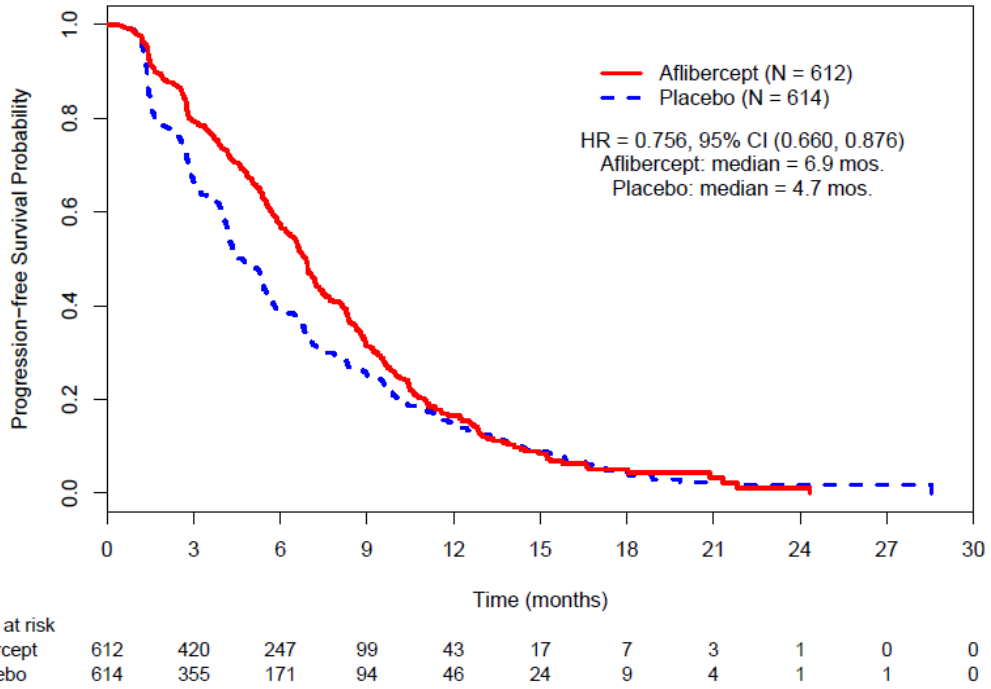
The VELOUR trial met its co-primary endpoints, demonstrating statistically significant and clinically meaningful increases in overall survival and progression-free survival. These results are summarized in the following table.

Efficacy Endpoints	Placebo/FOLFIRI (N=614)	ZALTRAP/FOLFIRI (N=612)
Overall Survival		
Number of deaths, 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)	0.82 (0.71 to 0.94)	
Stratified Log-Rank test p-value	0.0032	
Progression Free Survival (PFS)[a]		
Number of events, n (%)	454 (73.9%)	393 (64.2%)
Median PFS (95% CI) (months)	4.7 (4.2 to 5.4)	6.9 (6.5 to 7.2)
Stratified Hazard ratio (95% CI)	0.76 (0.66 to 0.87)	
Stratified Log-Rank test p-value [b]	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	

The Kaplan-Meier curves for overall survival and for progression-free survival abstracted from Dr. Zhang's review (Figures 2 and 4, respectively), are presented below



Planned subgroup analyses for overall survival based on stratification factors at randomization yielded an HR of 0.86 (95% CI: 0.68 to 1.1) in patients who received prior bevacizumab and an HR of 0.79 (95% CI: 0.67 to 0.93) in patients without prior bevacizumab exposure.



Patients at risk

Aflibercept	612	420	247	99	43	17	7	3	1	0	0
Placebo	614	355	171	94	46	24	9	4	1	1	0

8. Safety

The size of the safety of the safety database is adequate to identify serious risks and to ensure an adequate risk: benefit assessment. Evaluation of the safety of ziv-aflibercept was based primarily on data from three randomized trials (VELOUR, VITAL, and VANILLA) providing safety data on 1333 patients treated with ziv-aflibercept, supported by additional safety data from other Phase 1 and 2 trials for a total database of 2073 patients receiving ziv-aflibercept. The safety profile is consistent with other angiogenesis-inhibiting products, consisting of hypertension, proteinuria, hemorrhage, impairment of wound healing, viscus perforation and fistula formation, and dysphonia as well as an increase in the incidence of chemotherapy-related toxicities of neutropenia, thrombocytopenia, diarrhea, stomatitis, and palmar-plantar erythrodysesthesia. Based on these risks, and consistent with labeling for other products in this class, the product labeling will contain a Boxed Warning denoting the risks of hemorrhage with this product.

9. Advisory Committee Meeting

This application was not referred to an advisory committee. The review team concurred that the trial design and conduct were adequate, the primary efficacy endpoint was clinically important and relevant in this patient population and the treatment effect was robust, internally consistent across relevant subgroups and supported by demonstration of treatment effects on related efficacy endpoints, and that the safety profile was acceptable for this indication (treatment of metastatic colorectal cancer). Therefore, outside expertise was not necessary since there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

Colorectal cancer does not occur in children and necessary studies would be impossible or highly impracticable to perform. Therefore, a waiver to conduct pediatric studies under PREA was granted.

11. Labeling

- Proprietary name: The proposed proprietary name of Zaltrap was determined to be acceptable.

- Non-proprietary name: FDA determined that a unique nonproprietary name will be required for sanofi-aventis' Zaltrap (ziv-aflibercept), a biological product submitted in a 351(a) biologics license application (BLA) to distinguish the product from Eylea (aflibercept). A distinct nonproprietary name was required to minimize medication errors by (1) preventing patients from receiving a product different than what was intended to be prescribed, (2) reducing confusion among healthcare providers who may consider use of the same nonproprietary name to mean that the biological products are indistinguishable from a clinical standpoint, and to facilitate postmarketing safety monitoring by providing a clear means of determining which "aflibercept" product is dispensed to patients.

- Physician labeling: All major issues regarding the physician labeling have been resolved.

- Carton and immediate container labels: sanofi-aventis incorporated all FDA-requested carton and container labeling changes.

- Patient labeling/Medication guide: The clinical and safety reviewers agree that a Medication Guide is not required to ensure safe and effective use of ZALTRAP. Sanofi-aventis proposed patient labeling, however FDA considered this labeling unnecessary to enhance safe use and at FDA's request, the patient labeling was withdrawn. FDA's request was based on the determination that the product would be infused under the direct supervision of a healthcare provider in an office, clinic, or hospital-based setting, where patient counseling would be conveyed verbally and, potentially in writing, to the patient. In addition, it is unlikely that patient labeling would be provided to the patient, given that the product is not directly dispensed to the patient, but instead is prepared in a pharmacy that may be off-site.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.

- Risk Benefit Assessment
  Regular approval is sought for the ZALTRAP (ziv-aflibercept) for use in combination with irinotecan- and fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic colorectal cancer, a condition treated with cytotoxic chemotherapy for which 5 year survival is approximately 10% with standard treatment. This BLA relies primarily on the results a single, large, multicenter, placebo-controlled trial which provides substantial evidence of effectiveness based on demonstration of a clinically meaningful and robust improvement in overall survival, supported by statistically significant improvements in progression-free survival and objective tumor responses. In the current trial supporting the approval of ZALTRAP, 28% of patients received prior bevacizumab (in combination with oxalipatin.) Planned subgroup analyses for overall survival based on stratification factors at randomization yielded an HR of 0.86 (95% CI: 0.68 to 1.1) in patients who received prior bevacizumab and an HR of 0.79 (95% CI: 0.67 to 0.93) in patients without prior bevacizumab exposure. The safety profile is consistent with other angiogenesis-inhibiting products, consisting of hypertension, proteinuria, hemorrhage, impairment of wound healing, viscus perforation and fistula formation, and dysphonia as well as an increase in the incidence of chemotherapy-related toxicities of neutropenia, thrombocytopenia, diarrhea, stomatitis, and palmar-plantar erythrodysesthesia. The risks of ziv-aflibercept are acceptable in light of its benefits, the life-threatening nature of metastatic colorectal cancer, and the lack of satisfactory therapy for this population. The risk-benefit profile for ziv-aflibercept was also assessed by Drs. Keegan, Lemery, and Casak. All review disciplines recommend approval of this application, and I agree with their recommendations to approve this application.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies: None.

- Recommendation for other Postmarketing Requirements and Commitments: See action letter.

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/s/

TAMY E KIM
08/02/2012

RICHARD PAZDUR
08/02/2012