CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	November 18, 2011
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
BLA #	BLA 125387
Applicant Name	Regeneron Pharmaceuticals, Inc.
Date of Submission	February 17, 2011; received February 18, 2011
PDUFA Goal Date	November 18, 2011 (includes 3-month extension for major amendment)
Proprietary Name / Established/Proper Name	Eylea aflibercept
Dosage Forms / Strength	intravitreal injection 2 mg in 0.05 mL (40 mg/mL solution) in one single-use glass vial containing 0.278 mL of 40 mg/mL aflibercept (b) (4) vial)
Proposed Indication(s)	Treatment of patients with neovascular (wet) age-related macular degeneration (AMD)
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Sonal Wadhwa, Bill Boyd
Statistical Review	Dongliang Zhuang, Yan Wang, Mohammed Huque
Pharmacology Toxicology Review	Maria Rivera, William Taylor
OBP Review	Sarah Kennett, Sang Bong Lee, Chana Fuchs, Patrick Swann, Kathleen Clouse
Product Quality Microbiology Review	Reyes Candau-Chacon, Colleen Thomas, Kala Suvarna, Patricia Hughes
Project Manager's Review	Kimberly Rains
Clinical Pharmacology Review	Yongheng Zhang, Philip Colangelo
DSI	Kassa Ayalew, Susan Thompson
CDTL Reviews	William Boyd
Deputy Division Director's Review	Wiley Chambers
Division Director's Review	Renata Albrecht
OSE/DMEPA	Walter Fava, Carlos Mena-Grillasca, Carol Holquist
DPP Review	Christine Corser
OBP proper name memo	Kimberly Rains, Steve Kozlowski
Deputy Division Director memo on the proper name	Wiley Chambers

OND=Office of New Drugs
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Eylea (aflibercept) is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. It has been developed for the treatment of patients with Neovascular (wet) age-related macular degeneration (AMD). Other FDA-approved treatment options for wet AMD include: Visudyne (verteporfin for injection) approved in 2000, Macugen (pegaptanib sodium injection) approved in 2004, and Lucentis (ranibizumab injection) approved in 2006.

The review team has reviewed the issues in detail in their respective disciplines with regards to the safety and efficacy of aflibercept. For a detailed discussion of BLA 125387, the reader is referred to the individual discipline specific reviews. In addition Dr. Boyd's Cross-Discipline Team Leader Memorandum, Dr. Chambers's Deputy Division Director's Review, and Dr. Albrecht's Division Director Review also summarize key issues in the BLA submission. This memorandum will focus on selected issues from the BLA.

The Product Quality reviews from the Division of Monoclonal Antibodies, Office of Biotechnology Products (DMA/OBP) conclude that the data support that the manufacture of Eylea is well controlled and will lead to a product that is pure and potent. The DMA/OBP recommendation is for approval. Their recommendation follows the review of the data that constituted the major amendment leading to the 3-month clock extension for the BLA. The additional data reviewed during the extension were essential to the approval recommendation for the 2 mg in 0.05 mL (40 mg/mL solution) single-use glass vial (b) (4) vial). There are also six Product Quality postmarketing commitments that will accompany the approval.

The Product Quality Microbiology reviewers have recommended approval based on their review of the drug substance and drug product for the amended application for the 40mg/mL (b) (4) vial. The recommendation for approval is accompanied by a postmarketing commitment for at-scale hold time validation studies.

The facilities have been found to be in compliance with cGMPs.

The proper name of Eylea received considerable attention during the review. This issue is discussed in Kimberly Rains's memorandum of November 17, 2011 and Dr. Chambers's memorandum of November 16, 2011. As part of our evaluation, we have discussed the proper name for this BLA product with OBP, OCC, DMEPA and others. In my evaluation of this issue, I have carefully considered the issues and points discussed in the memorandums, the discussions on this topic, and the points raised by Regeneron. I concur with Kimberly Rains's memorandum with the recommendation that the proper name for the product should be aflibercept. A proper name of aflibercept (not including the dosage form in the proper name) for Eylea is consistent with Agency's longstanding practice for biological products licensed under section 351 of the PHSA that are reviewed by the Center for Biologics Evaluation and Research (CBER), and the vast majority of such products reviewed by the Center for Drug Evaluation and Research (CDER). In addition, the potential for medication errors was raised as part of these discussions. If another formulation of aflibercept intended for injection were approved in the future and was not appropriate for intravitreal injection, there is a potential for medication errors.

The recommendation from the pharmacology/toxicology reviewer is for approval. The Clinical Pharmacology reviewer finds the data in the application acceptable. Eylea is labeled as Pregnancy Category C.

In support of the evaluation of Eylea for the treatment of patients with wet AMD, the applicant performed two randomized phase 3 trials that compared three dosing regimens of aflibercept to ranibizumab. The three dosing regimens of aflibercept were 2 mg of aflibercept administered every 4 weeks (2Q4), 0.5 mg of aflibercept administered every 4 weeks (0.5Q4), and 2 mg of aflibercept administered every 8 weeks (2Q8) following 3 initial monthly doses given every 4 weeks (a sham injection at interim 4-week visits was utilized to maintain masking to treatment arm). The ranibizumab comparator dosing regimen was 0.5 mg ranibizumab administered every 4 weeks (RQ4). The primary endpoint in the studies was the proportion of patients maintaining vision at week 52 (defined as a loss of visual acuity of less than 15 letters in the ETDRS letter score compared to baseline). In both trials, the aflibercept dosing regimens were found to be non-inferior to RQ4. The efficacy results were within the pre-specified 10% non-inferiority (NI) margin. The NI margin is based on the demonstrated effectiveness of ranibizumab. The recommended dosing regimen for aflibercept is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). The product labeling also notes that although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

The safety evaluation of aflibercept includes data from over 1800 patients who received aflibercept in the two phase 3 studies. The commonly reported adverse effects in Eylea recipients included conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure. Assessments were made for nasomucosal alterations in a subset of patients (ENT sub-study) in order to follow-up on findings from toxicology studies in animals that noted nasal erosions and ulcerations. The ENT sub-study found similar numbers of nasal mucosal treatment emergent AEs for aflibercept and comparator treated patients. Adverse effects were similar for aflibercept and ranibizumab treated patients. The product labeling contraindicates use in patients with ocular or periocular infections, active ocular inflammation, or hypersensitivity. There are also Warnings and Precautions informing of the risk for (1) endophthalmitis and retinal detachments; adverse effects associated with intravitreal injections; (2) increased intraocular pressure following intravitreal injection; and (3) potential risk for thromboembolic events associated with the use of VEGF inhibitors.

The application for Eylea (aflibercept) was presented to the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) on June 17, 2011. The committee voted unanimously (10 Yes; 0 No) that the product demonstrated efficacy and safety in neovascular AMD, and recommended the 2 mg every 8 weeks dosing regimen (after 3 loading doses given every 4 weeks) . There was discussion that information on injections every 4 weeks could also be included in labeling to allow for some degree of flexibility on the timing of follow-up injections.

Age-related macular degeneration is a disease of adults. The application was discussed at a meeting of the Pediatric Review Committee (PERC) on June 1, 2011, and the application was granted a pediatric waiver because the disease only occurs in adults.

The proposed proprietary name, Eylea, has been found to be acceptable. A recent re-evaluation of the proposed proprietary name on November 4, 2011, did not identify any new conflicts.

In summary, the overall benefits and risk and the product quality assessment support the approval of BLA 125387. The product labeling adequately describes the safety and efficacy findings. The approval is accompanied by one postmarketing requirement to evaluate the effect of aflibercept on corneal endothelial cells after at least one year of treatment and 7 postmarketing commitments (6 commitments related to product quality and 1 related to product quality microbiology).

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