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APPLICATION NUMBER:

125387Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products[1]
Subject	Division Director Summary Review
BLA Number	BLA 125387
Related INDs **Other IND**	IND 12462 for wet age-related macular degeneration (b) (4) IND (b) (4) IND (b) (4)
Applicant Name	Regeneron Pharmaceuticals Inc
Date of Submission **Date of Receipt**	February 17, 2011 February 18, 2011
PDUFA Goal Date	August 18, 2011
Major Amendment	August 12, 2001
Revised PDUFA Goal Date	November 18, 2011
Proprietary Name / **Established (USAN) Name**	Eylea™ aflibercept
Formulation **Dose**	(Ophthalmic) 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 for NME	*Approval*

[1] The Office of Antimicrobial Products was reorganized effective May 2011; specifically the Division of Special Pathogen and Transplant Products (DSPTP) and Division of Anti-Infective and Ophthalmology Products (DAIOP) were reorganized into the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Anti-Infective Products (DAIP).

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Sonal Wadhwa, Bill Boyd, Wiley Chambers 7/2011
CDTL Review	Bill Boyd
Deputy Director	Wiley Chambers
Statistical Review	Dongliang Zhuang, Yan Wang, Mohammed Huque 7/2011
Pharmacology/Toxicology Review	Maria Rivera, William Taylor 7/2011
Clinical Pharmacology Review	Yongheng (Eric) Zhang, Philip Colangelo 7/2011
Product Quality Reviews OPS/OBP/DMA	Sarah Kennett, Sang Bong Lee, Chana Fuchs, Patrick Swann, Kathleen Clouse 11/10/2011
Quality Microbiology Reviews OC/OMPQ/DGMPA/BMAB	Reyes Candau-Chacon, Colleen Thomas, Kala Suvarna, Patricia Hughes 10/11/2011
OC/Facilities Inspection	Mahesh Ramanadham 11/14/2011 via email
OSI/DGCPC	Kassa Ayalew, Susan Thompson 11/2/2011
OSE/DMEPA Proprietary Name	Walter Fava, Carlos Mena-Grillasca, Carol Holquist 11/4/2011
OBP Review Name, carton/container label	Kimberly Rains, Sarah Kennett, Patrick Swann 8/30/2011
OSE/DMEPA Labeling Review	Walter Fava, Carlos Mena-Grillasca, Carol Holquist 8/5/2011
OPDP/DPP (formerly DDMAC)	Christine Corser 10/13/2011
Pediatric Review Committee	Pediatric studies waived 6/17/2011
Advisors and Consultants Staff	Yvette Waples 6/17/2011

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OC/OMPQ/DGMPA/BMAB=Office of Compliance, Office of Manufacturing Product Quality, Division of Good Manufacturing Practice Assessment, Biotech Manufacturing Assessment Branch; formerly OC/DMPQ/MAPCB/BMT = Office of Compliance/Division of Manufacturing and Product Quality/Manufacturing and Pre Approval Chemistry Branch/ Biologics Microbiology Team
OPS/OBP/DMA = Office of Pharmaceutical Sciences/Office of Biologics Products/Division of Monoclonal Antibodies
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OPDP/DPP=Office of Prescription Drug Promotion/Division of Professional Promotion; formerly, DDMAC=Division of Drug Marketing, Advertising and Communication
PMHT=Pediatric and Maternal Health Staff

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1. Summary and Recommendations

Aflibercept is a human fusion protein that is proposed for the treatment of neovascular (wet) age-related macular degeneration (AMD), given in a regimen of 2 mg (0.05 mL of 40 mg/mL solution) by intravitreous injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg via intravitreal injection once every 8 weeks (2 months). Dosing can be given as frequently as every 4 weeks based on the results of both Phase 3 studies, but no added benefit was seen with more frequent dosing. Injection must be administered by a qualified physician under aseptic conditions including surgical hand disinfection, sterile gloves, drape and eyelid speculum. The product is supplied in a single-use sterile glass vial with a (b) (4) stopper and an aluminum crimp seal.

Based on the review of BLA 125387, the product quality reviewers and the product microbiology sterility reviewers identified multiple deficiencies during the initial 6 month review period that needed to be resolved before the application could be approved. Regeneron provided multiple submissions to address these issues, including a major amendment submitted on August 12, 2011. The FDA accepted this major amendment for review and issued a letter on August 17, 2011 extending the PDUFA goal date from August 18, 2011 to November 18, 2011, to provide time for review of the major amendment. In addition, Regeneron amended the BLA (b) (4) single-use vial to be reviewed for approval during the extended review cycle. Because the list of outstanding deficiencies identified during the first six months of the review cycle was extensive, the Product Quality review staff and Regeneron held biweekly teleconferences from August through October 2011 during which all deficiencies were systematically discussed and Regeneron provided the information and documentation necessary to address each of the deficiencies. In addition to addressing the Product Quality deficiencies, Regeneron agreed to six post-marketing commitments (PMC) from Product Quality and one PMC from Quality Microbiology that are summarized in Section 1.2 and itemized in Section 13.3.

Other disciplines, including clinical, statistical, pharmacology/toxicology, clinical pharmacology, recommended approval of the application.

Review of the package insert, carton and container labeling was undertaken and included comments from each of the review disciplines as well as staff from DMEPA, OPDP/DPP and OBP. The trade name Eylea was found acceptable by DMEPA. The proper name[2] was designated as aflibercept.

The Office of Scientific Investigations recommended that clinical trial data and sponsor inspections are acceptable.

[2] Biologics regulations refer to the name of the active ingredient as the proper name, for small molecules the name of the product is called the established name and includes the active moiety and dosage form.

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