CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125387Orig1s020

Trade Name:	EYLEA
Generic or Proper Name:	Aflibercept
Sponsor:	Regeneron Pharmaceuticals, Inc.
Approval Date:	June 7, 2013
Indication:	For the treatment of patients with: • Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Central Retinal Vein Occlusion (CRVO)

CENTER FOR DRUG EVALUATION AND RESEARCH

125387Orig1s020

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s020

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125387/S-015
BLA 125387/S-020

SUPPLEMENT APPROVAL

Regeneron Pharmaceuticals, Inc.
Attention: Jennifer Woo, Ph.D., PPM, RAC
Regulatory Associate IV
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Woo:

Please refer to the following Supplemental Biologics License Applications (sBLAs), submitted under section 351(a) of the Public Health Service Act for EYLEA (aflibercept) Injection:

Supplement Number	Date Submitted	Date Received
S-015	August 10, 2012	August 10, 2012
S-020	October 5, 2012	October 5, 2012

Supplement-015, submitted as a "Changes Being Effected" supplemental biologics application, proposed the addition of (b) (4)

Supplement-020, submitted as a "Prior Approval" supplemental biologics application, provides for revisions to Section 6.2 Clinical Studies Experience, the deletion of (b) (4) , and updates to Section 8.1 Pregnancy with data from a recently completed reproductive toxicity study. We acknowledge receipt of your amendment to S-020 dated April 24, 2013. This submission constituted a complete response to our April 5, 2013, action letter for S-020.

We have completed our review of these supplemental applications, as amended. The proposed changes in S-020 supersede the changes proposed in S-015. S-020 is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revision listed below and incorporated in the enclosed labeling:

> In Section 16 How Supplied/Storage and Handling, revise the first statement of the carton contents to read, "one single-use, sterile, 3-mL, glass vial designed to deliver 0.05 mL of 40 mg/mL EYLEA."

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions regarding these supplemental applications, please contact Ms. Leanna M. Kelly, Consumer Safety Officer, at (301) 796-0471. For all other inquiries regarding this BLA, call Mr. Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
06/07/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s020

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125387/S-020

COMPLETE RESPONSE

Regeneron Pharmaceuticals, Inc.
Attention: Laura Pologe, Ph.D.
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Pologe:

Please refer to your Supplemental Biologics License Application (sBLA) dated and received October 5, 2012, submitted under section 351(a) of the Public Health Service Act for EYLEA (aflibercept) Injection.

We acknowledge receipt of your amendment dated February 14, 2013.

This "Prior Approval" labeling supplement to your biologics license application proposes to revise Section 6.2 Clinical Studies Experience, to delete (b) (4), and to update Section 8.1 Pregnancy with data from a recently completely reproductive toxicity study.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. Your proposed edits to Section 8.1 Pregnancy do not accurately describe the new embryofetal data.

Please submit draft labeling that is consistent with the attached labeling. In addition, submit updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the supplemental application. A resubmission

must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on "Formal Meetings Between FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions regarding this supplemental application, please contact Ms. Leanna M. Kelly, Consumer Safety Officer, at (301) 796-0471. For all other inquiries regarding this BLA, call Mr. Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Labeling

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
04/05/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s020

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.

EYLEA™ (aflibercept) Injection
For Intravitreal Injection
Initial U.S. Approval: 2011

----------RECENT MAJOR CHANGES----------
- Indications and Usage, Macular Edema Following Central Retinal Vein Occlusion (CRVO) (1.2) 9/2012
- Dosage and Administration, Macular Edema Following Central Retinal Vein Occlusion (CRVO) (2.3) 9/2012
- Dosage and Administration, Preparation for Administration (2.4) 9/2012
- Contraindications, Hypersensitivity (4.3) 9/2012
- Warnings and Precautions, Thromboembolic Events (5.3) 9/2012

----------INDICATIONS AND USAGE----------
EYLEA is indicated for the treatment of patients with:
- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Central Retinal Vein Occlusion (CRVO) (1.2)

----------DOSAGE AND ADMINISTRATION----------
For ophthalmic intravitreal injection only. (2.1)

Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.2)
- 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. (2.2)

Macular Edema Following Central Retinal Vein Occlusion (CRVO)
- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly). (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
40 mg/mL solution for intravitreal injection in a single-use vial (3)

----------CONTRAINDICATIONS----------
- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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1.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)
2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
2.3 Macular Edema Following Central Retinal Vein Occlusion (CRVO)
2.4 Preparation for Administration
2.5 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
4.2 Active Intraocular Inflammation
4.3 Hypersensitivity
5 WARNINGS AND PRECAUTIONS
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***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY. EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The recommended dose for EYLEA 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). 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 [*see Clinical Studies (14.1)*].

2.3 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly) [*see Clinical Studies (14.2)*].

2.4 Preparation for Administration

EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

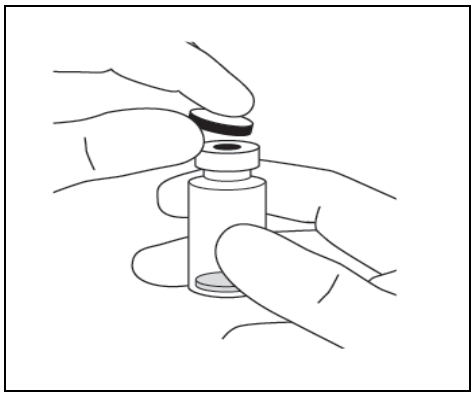
Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle.

Vial

The glass vial is for single use only.

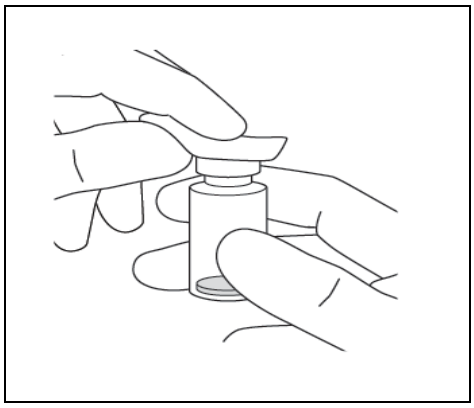
1. Remove the protective plastic cap from the vial (see Figure 1).

Figure 1:



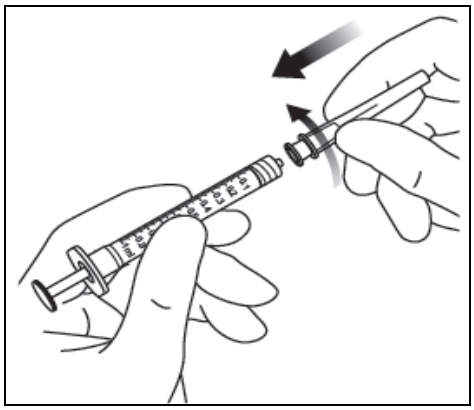
2. Clean the top of the vial with an alcohol wipe (see Figure 2).

Figure 2:



3. Remove the 19-gauge x 1½-inch, 5-micron, filter needle from its pouch and remove the 1-mL syringe supplied in the carton from its pouch. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see Figure 3).

Figure 3:



4. Push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.

5. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid (see Figures 4a and 4b).

Figure 4a:

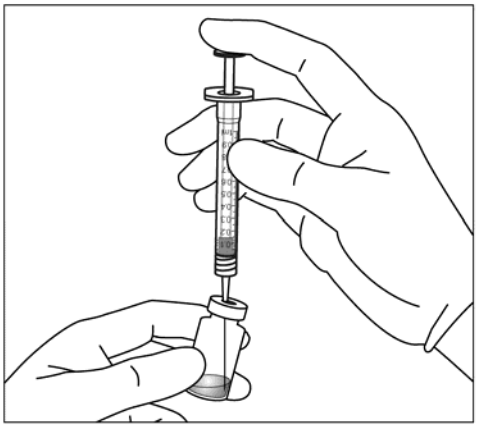
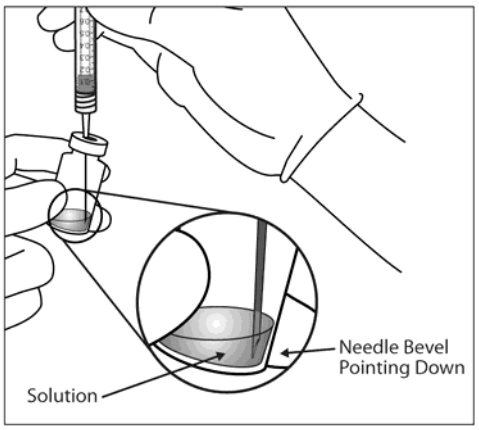


Figure 4b:

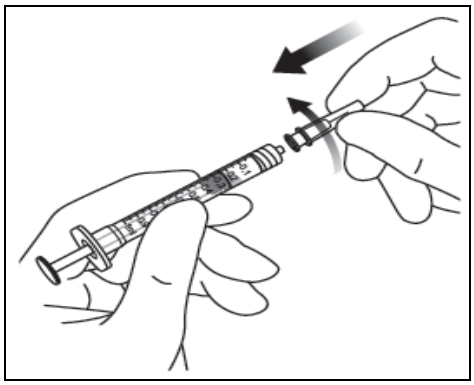


6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

7. Remove the filter needle from the syringe and properly dispose of the filter needle.
Note: Filter needle is **not** to be used for intravitreal injection.

8. Remove the 30-gauge x ½-inch injection needle from the plastic pouch and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 5).

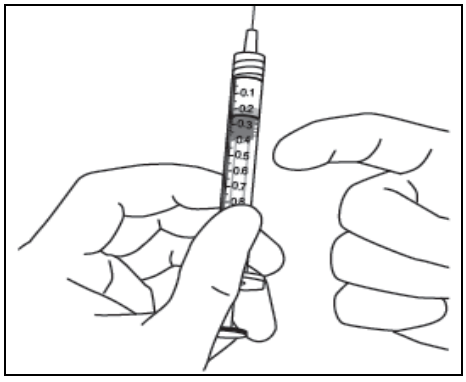
Figure 5:



9. When ready to administer EYLEA, remove the plastic needle shield from the needle.

10. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).

Figure 6:



11. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe (see Figures 7a and 7b).

Figure 7a:

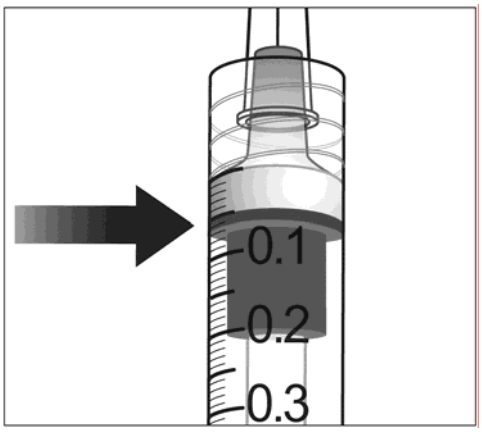
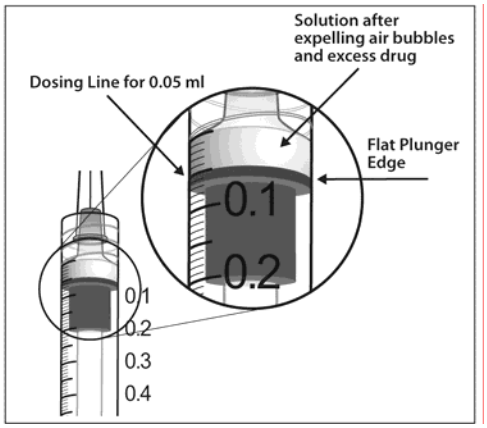


Figure 7b:



2.5 Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay [*see Patient Counseling Information (17)*].

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution for intravitreal injection.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.5) and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.5)*].

5.3 Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence in the VIEW1 and VIEW2 wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA [*see Clinical Studies (14.1)*]. The incidence in the COPERNICUS and GALILEO CRVO studies during the first 6 months was 0% (0/218) in

patients treated with EYLEA 2 mg every 4 weeks compared with 1.4% (2/142) in patients receiving sham treatment [*see Clinical Studies (14.2)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions (5)* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

6.1 Injection Procedure

Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis, traumatic cataract, increased intraocular pressure, and vitreous detachment.

6.2 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2042 patients treated with EYLEA constituted the safety population in four phase 3 studies. Among those, 1441 patients were treated with the recommended dose of 2 mg.

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months [*see Clinical Studies (14.1)*].

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Conjunctival hyperemia	4%	8%
Corneal erosion	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were retinal detachment, retinal tear, and endophthalmitis. Hypersensitivity has also been reported in less than 1% of the patients treated with EYLEA.

Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The data described below reflect exposure to EYLEA in 218 patients with macular edema following CRVO treated with 2 mg dose in 2 double-masked, controlled clinical studies (COPERNICUS and GALILEO) for 6 months [*see Clinical Studies (14.2)*].

Table 2: Most Common Adverse Reactions (≥1%) in CRVO Studies

Adverse Reactions	EYLEA (N=218)	Control (N=142)
Eye pain	13%	5%
Conjunctival hemorrhage	12%	11%
Intraocular pressure increased	8%	6%
Corneal erosion	5%	4%
Vitreous floaters	5%	1%
Conjunctival hyperemia	5%	3%
Foreign body sensation in eyes	3%	5%
Vitreous detachment	3%	4%
Lacrimation increased	3%	4%
Injection site pain	3%	1%
Vision blurred	1%	<1%
Intraocular inflammation	1%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were cataract, eyelid edema, corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD and CRVO studies, the pre-treatment incidence of immunoreactivity to EYLEA was 1% to 3% across treatment groups. After dosing with EYLEA for 52 weeks (wet AMD), or

24 weeks (CRVO), antibodies to EYLEA were detected in a similar percentage range of patients. Both in the wet AMD and in the CRVO studies, there were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

In the clinical studies, approximately 85% (1728/2034) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 58% (1177/2034) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

11 DESCRIPTION

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 formulated as an iso-osmotic solution for intravitreal administration. 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. Aflibercept is produced in recombinant Chinese hamster ovary (CHO) cells.

EYLEA is a sterile, clear, and colorless to pale yellow solution. EYLEA is supplied as a preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL (50 microliters) of EYLEA (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

12.2 Pharmacodynamics

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

In the clinical studies anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52. Anatomic data were not used to influence treatment decisions. [*see Clinical Studies (14.1)*].

Macular Edema Following Central Retinal Vein Occlusion (CRVO)

Reductions in mean retinal thickness were observed in COPERNICUS and GALILEO at Week 24 compared to baseline. Anatomic data were not used to influence treatment decisions. [*see Clinical Studies (14.2)*].

12.3 Pharmacokinetics

EYLEA is administered intravitreally to exert local effects in the eye. In patients with wet AMD or CRVO, following intravitreal administration of EYLEA, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept: VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept: VEGF complex).

Absorption/Distribution

Following intravitreal administration of 2 mg per eye of EYLEA to patients with wet AMD and CRVO, the mean C_{max} of free aflibercept in the plasma was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL) and 0.05 mcg/mL (range 0 to 0.081 mcg/mL), respectively and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeated doses intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100 fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

The volume of distribution of free aflibercept following intravenous (I.V.) administration of aflibercept has been determined to be approximately 6L.

Metabolism/Elimination

Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The terminal elimination half-life (t1/2) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.

Specific Populations

Renal Impairment

Pharmacokinetic analysis of a subgroup of patients (n=492) in one wet AMD study, of which 43% had renal impairment (mild n=120, moderate n=74, and severe n=16), revealed no differences with respect to plasma concentrations of free aflibercept after intravitreal administration every 4 or 8 weeks. Similar results were seen in patients in a CRVO study. No dose adjustment based on renal impairment status is needed for either wet AMD or CRVO patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at weekly doses ranging from 3 to 30 mg per kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. A No Observed Adverse Effect Level (NOAEL) was not identified. Intravenous administration of the lowest dose of aflibercept assessed in monkeys (3 mg per kg) resulted in systemic exposure (AUC) that was approximately 1500 times higher than the systemic exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible within 20 weeks after cessation of treatment.

13.2 Animal Toxicology and/or Pharmacology

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2 or 4 mg per eye. At the NOAEL of 0.5 mg per eye in monkeys, the systemic exposure (AUC) was 56 times higher than the exposure observed in humans after an intravitreal dose of 2 mg. Similar effects were not seen in clinical studies [*see Clinical Studies (14)*].

14 CLINICAL STUDIES

14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with EYLEA) in the two studies (VIEW1 and VIEW2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); 3) EYLEA 0.5 mg administered every 4 weeks (EYLEA 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). Patient ages ranged from 49 to 99 years with a mean of 76 years.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Data are available through week 52. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group.

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 3 and Figure 8 below.

Table 3: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies

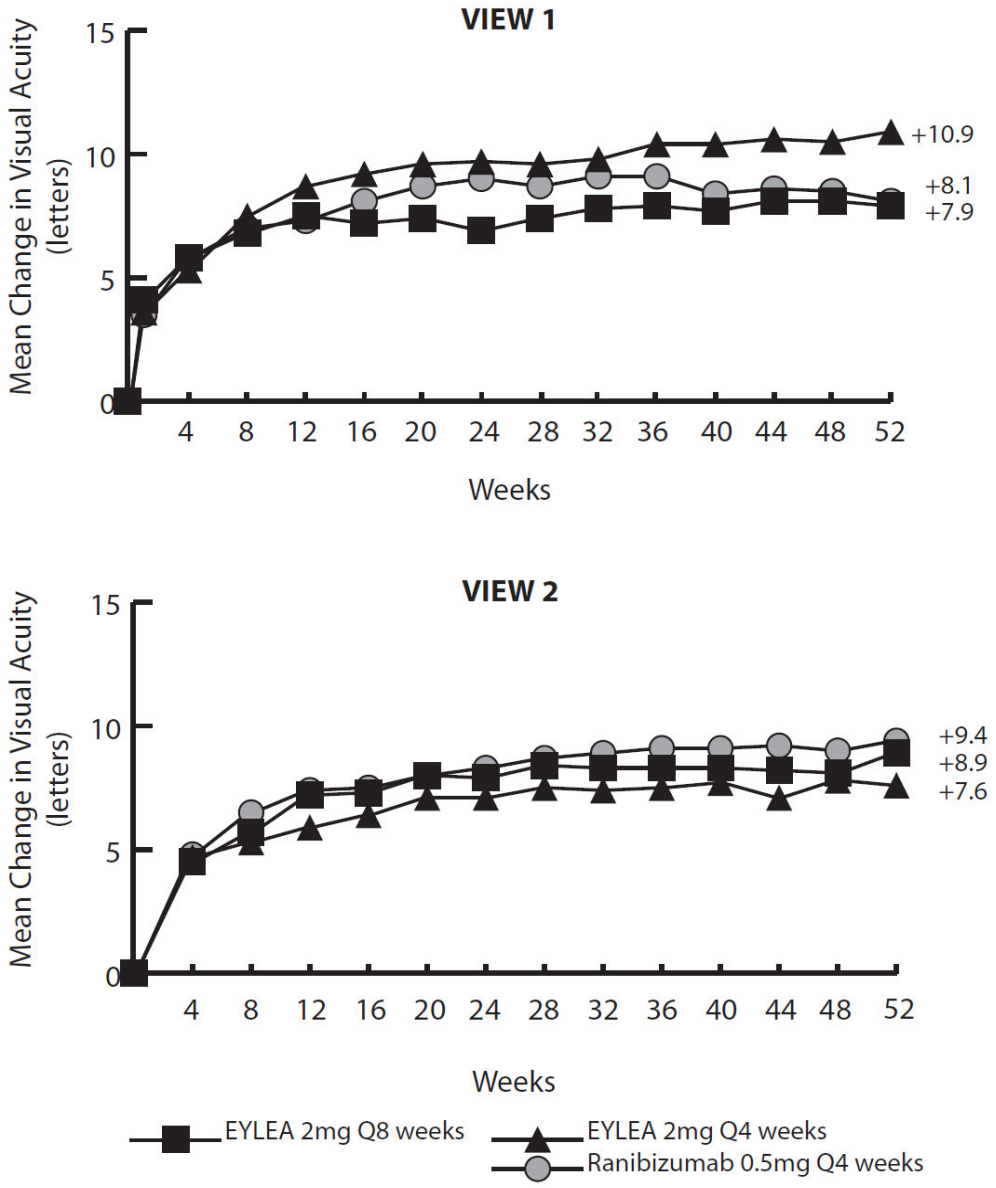
	VIEW1			VIEW2		
	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
Efficacy Outcomes						
Proportion of patients who maintained visual acuity (%) (<15 letters of BCVA loss)	94%	95%	94%	95%	95%	95%
Difference[b] (%) (95.1% CI)	0.6 (-3.2, 4.4)	1.3 (-2.4, 5.0)		0.6 (-2.9, 4.0)	-0.3 (-4.0, 3.3)	
Mean change in BCVA as measured by ETDRS letter score from Baseline	7.9	10.9	8.1	8.9	7.6	9.4
Difference[b] in LS mean (95.1% CI)	0.3 (-2.0, 2.5)	3.2 (0.9, 5.4)		-0.9 (-3.1, 1.3)	-2.0 (-4.1, 0.2)	
Number of patients who gained at least 15 letters of vision from Baseline (%)	92 (31%)	114 (38%)	94 (31%)	96 (31%)	91 (29%)	99 (34%)
Difference[b] (%) (95.1% CI)	-0.4 (-7.7, 7.0)	6.6 (-1.0, 14.1)		-2.6 (-10.2, 4.9)	-4.6 (-12.1, 2.9)	

BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = Last Observation Carried Forward (baseline values are not carried forward); 95.1% confidence intervals were presented to adjust for safety assessment conducted during the study.

[a] After treatment initiation with 3 monthly doses

[b] EYLEA group minus the ranibizumab group

Figure 8: Mean Change in Visual Acuity from Baseline to Week 52 in VIEW1 and VIEW2 Studies



14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, sham-controlled studies in patients with macular edema following CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with EYLEA) in the two studies (COPERNICUS and GALILEO). In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4), or sham injections (control group)

administered every 4 weeks for a total of 6 injections. Patient ages ranged from 22 to 89 years with a mean of 64 years.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the EYLEA 2 mg Q4 group was superior to the control group for the primary endpoint.

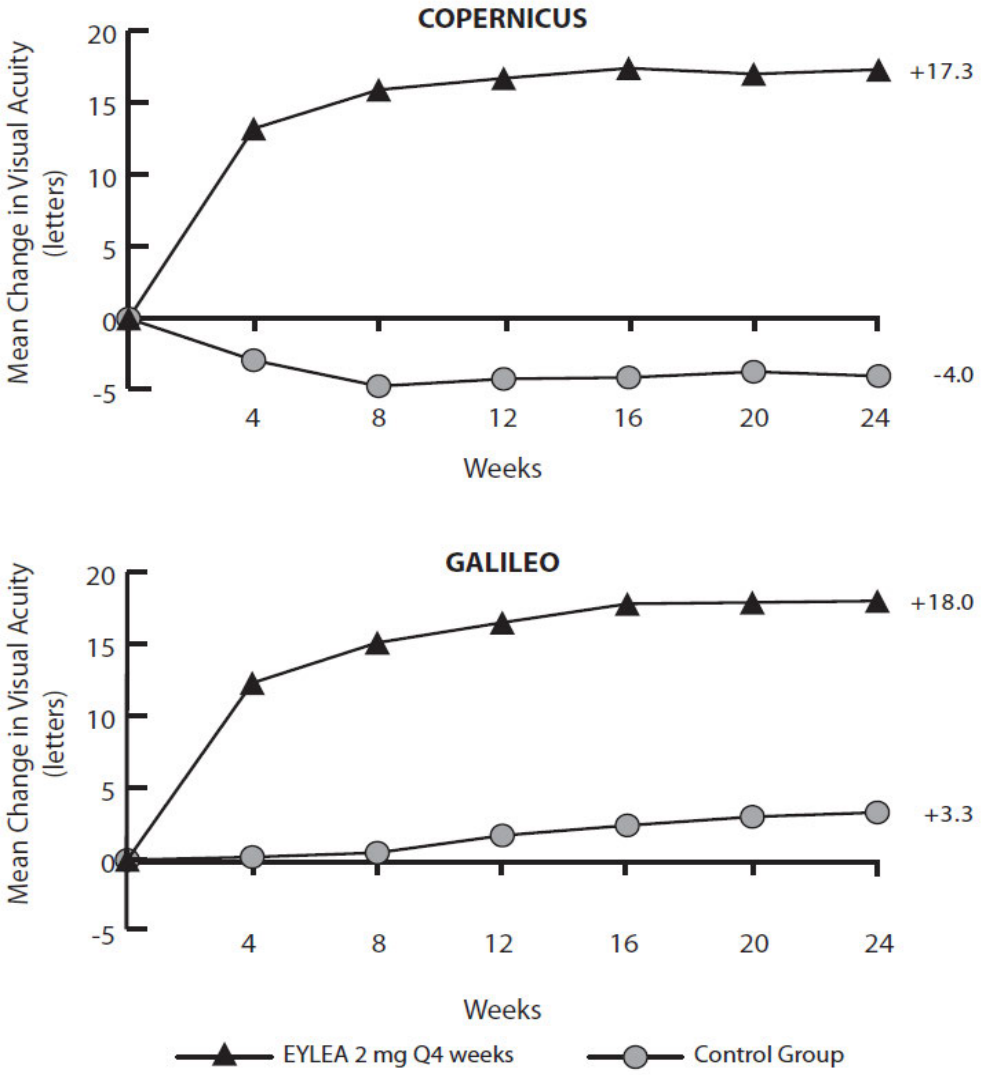
Results from the analysis of the COPERNICUS and GALILEO studies are shown in Table 4 and Figure 9 below.

Table 4: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in COPERNICUS and GALILEO Studies

	COPERNICUS		GALILEO	
	Control	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q4 weeks
	N=73	N=114	N=68	N=103
Efficacy Outcomes				
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	12%	56%	22%	60%
Weighted Difference [a,b] (%) (95.1% CI)		44.8%[c] (32.9, 56.6)		38.3%[c] (24.4, 52.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	-4.0 (18.0)	17.3 (12.8)	3.3 (14.1)	18.0 (12.2)
Difference in LS mean [a,d] (95.1% CI)		21.7[c] (17.3, 26.1)		14.7[c] (10.7, 18.7)

[a] Difference is EYLEA 2 mg Q4 weeks minus Control
[b] Difference and CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for baseline factors; 95.1% confidence intervals were presented to adjust for the multiple assessments conducted during the study.
[c] $p<0.01$ compared with control
[d] LS mean and CI based on an ANCOVA model

Figure 9: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in COPERNICUS and GALILEO Studies



Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity, retinal perfusion status, and CRVO duration) in each study and in the combined analysis were in general consistent with the results in the overall populations.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each Vial is for single eye use only. EYLEA is supplied in the following presentation [*see Dosage and Administration (2.4) and (2.5)*].

NDC NUMBER	CARTON TYPE	CARTON CONTENTS
61755-005-02	Vial	one single-use, sterile, 3-mL, glass vial designed to deliver 0.05 mL of 40 mg/mL EYLEA one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents one 30-gauge x ½-inch injection needle for intravitreal injection one 1-mL syringe for administration one package insert

Storage

EYLEA should be refrigerated at 2°C to 8ºC (36°F to 46ºF). Do Not Freeze. Do not use beyond the date stamped on the carton and container label. Protect from light. Store in the original carton until time of use.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patient to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
U.S. License Number 1760
EYLEA™ is a registered trademark of Regeneron Pharmaceuticals, Inc.

Issue Date: month 201X
Initial U.S. Approval: 2011
Regeneron U.S. Patents 7,306,799; 7,531,173; 7,608,261; 7,070,959; 7,374,757; 7,374,758, and other pending patents

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s020

CLINICAL REVIEW(S)

Clinical Review of BLA 125387
Prior Approval Labeling Supplement

BLA 125387/S-020
eCTD 0092

Submission Date: April 24, 2013
Receipt Date: April 25, 2013
Review Date: April 30, 2013

Applicant: Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Applicant's Representative: Laura Pologe, Ph.D.
Associate Director, Regulatory Affairs
914-847-7926

Drug: EYLEA (aflibercept) Injection

Pharmacologic Category: anti-VEGF monoclonal antibody

Submitted:
The applicant has submitted an amendment, eCTD 0092, to a Prior Approval Labeling Supplement (S-020) for revisions to Section 6.2 Clinical Studies Experience, to delete (b) (4) , and to update Section 8.1 Pregnancy with data from a recently completed reproductive toxicity study.

Supplement-020 received a Complete Response letter on April 5, 2013. The applicant's proposed edits to Section 8.1 Pregnancy did not accurately describe the new embryofetal data.

The applicant submitted an amendment, eCTD 0092, on April 24, 2013, incorporating the Division's recommended changes. This submission constitutes a complete response to action for S-020.

Following is the Division's recommended labeling for EYLEA that was attached to the April 4, 2013, Complete Response letter for S-020.

Applicant proposed additions are noted by underline and deletions by within the review.
Reviewer proposed additions are noted by underline and deletions by within the review.

Deleted: strikethrough
Deleted: strikethrough

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEANNA M KELLY
05/06/2013

SONAL D WADHWA
05/06/2013

WILLIAM M BOYD
05/06/2013

Clinical Review of BLA 125387
Prior Approval Labeling Supplement

BLA 125387/S-020

eCTD 0078	**Submission Date:**	October 5, 2012
	Receipt Date:	October 5, 2012
eCTD 0089	**Submission Date:**	February 14, 2013
	Receipt Date:	February 24, 2013
	Review Date:	March 22, 2013

Applicant: Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Applicant's Representative: Laura Pologe, Ph.D.
Associate Director, Regulatory Affairs
914-847-7926

Drug: EYLEA (aflibercept) Injection

Pharmacologic Category: anti-VEGF monoclonal antibody

Submitted:
The applicant has submitted a Prior Approval Labeling Supplement for revisions to Section 6.2 Clinical Studies Experience, to delete (b) (4), and to update Section 8.1 Pregnancy with data from a recently completed reproductive toxicity study.

The applicant submitted an amendment, eCTD 0089, on February 14, 2013, to append (b) (4) (b) (4) (b) (4)
No new changes were proposed to the labeling in this amendment.

Following is the current approved labeling for EYLEA.

Applicant proposed additions are noted by underline and deletions by within the review. Deleted: strikethrough
Reviewer proposed additions are noted by underline and deletions by within the review. Deleted: strikethrough

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's Comments:

The labeling submitted by the applicant on October 5, 2012, is not acceptable. The changes shown throughout this review should be made.

The applicant submitted a CBE Supplement, Supplement-015, on August 10, 2012, for the addition of (b) (4) *No action was taken on Supplement-015.*

In the current submission for Supplement-020, the applicant proposes to delete (b) (4) *and add the term, "intraocular inflammation" to Section 6.2 Clinical Studies Experience. This proposal supersedes the applicant's previous proposal in Supplement-015 to add* (b) (4) (b) (4) (b) (4) (b) (4) *This change is acceptable.*

Recommendations:

This supplement is not recommended for approval. Draft labeling consistent with the labeling found in this review should be communicated to the applicant.

Leanna Kelly
Consumer Safety Officer

Sonal Wadhwa, M.D.
Medical Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEANNA M KELLY
04/05/2013

SONAL D WADHWA
04/05/2013

WILLIAM M BOYD
04/05/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s020

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	125387\20
Supporting document/s:	SN 0078 and SN 0089
Applicant's letter date:	SN 0078/October 5, 2012
	SN 0089/February 14, 2013
CDER stamp date:	SN 0078/October 5, 2012
	SN 0089/February 14, 2013
Product:	EYLEA (Aflibercept Ophthalmic Solution)
Indication:	Neovascular "wet" age-related macular degeneration (AMD)
Applicant:	Regeneron Pharmaceuticals, Inc.
Review Division:	Transplant and Ophthalmology Products
Reviewer:	María I. Rivera, Ph.D.
Supervisor/Team Leader:	Lori Kotch, Ph.D.
Division Director:	Renata Albrecht, M.D.
Project Manager:	Michael Puglisi

In SN-0078, Regeneron proposed a revision to sections 6.2 (ADR tables) to add intraocular inflammation, (b) (4) (b) (4) 8.1 (Pregnancy) to add updated information from a completed embryofetal development toxicology study (# VGFT-T-11034)

In SN-0089, Regeneron is submitting an amendment to the prior approval labeling supplement (SN-0078) to remove (b) (4) (b) (4).

Sponsor's proposed label:

Regeneron proposes the following label changes based on the results of the new embryofetal development study. Italic font in the sponsor's proposed label indicates new information added by the sponsor to the initially approved EYLEA label.

8.1 Pregnancy

Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered during organogenesis in pregnant rabbits at intravenous doses ~~of~~ (b) (4)

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

(b) (4)

Reviewer's changes to proposed label:

This reviewer recommends the following edits to the sponsor's proposed label to accommodate a decrease in the previously established exposure margins, given the new embryofetal data. Additionally the proposed edits attempt to maintain consistency with information included in the label for Zaltrap (intravenous aflibercept).

Pregnancy Category C. *Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every 6 six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical*

hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In addition, this reviewer recommends the following changes to Sections 13.1 and 13.2 of the current EYLEA label. Bold font indicates new information added by the reviewer.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at weekly doses ranging from 3 to 30 mg per kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. A No Observed Adverse Effect Level (NOAEL) was not identified. (b) (4)

(b) (4)

the lowest dose of aflibercept assessed in monkeys (3 mg per kg) resulted in systemic exposure (AUC) that was approximately 1500 times higher *than the* ***systemic*** *exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible* ***within 20 weeks after cessation of treatment****.*

13.2 Animal Toxicology and/or Pharmacology

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2 or 4 mg per eye. At the NOAEL of 0.5 mg per eye in monkeys, the systemic exposure (AUC) was (b) (4) *56 times higher* (b) (4)

[redacted] *than the exposure observed in humans after an intravitreal dose of 2 mg. Similar effects were not seen in clinical studies [see Clinical Studies (14)].*

Study title: AVE005: Prenatal Developmental Toxicity Study in Rabbits after Subcutaneous Administration

Study no.:	VGFT-TX-11034 (T2082408)
Study report location:	Module 4.2.3.5.2
Conducting laboratory and location:	[redacted]
Date of study initiation:	Jul 21, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	[redacted] (VEGF Trap), Filled Drug Product Batch #: C08002M640R13, Labeled Drug Product Batch #: 9003300001 [redacted]% pure (total protein content)

Key Study Findings

- A treatment related effect on malformations was observed at all dose levels (cardiac ventricular septal defects with/without malformation of major vessels and skeletal malformations at all doses; two fetuses with spina bifida and multiple malformations at 0.1 mg/kg; one fetus with encephalo-meningocele at 1 mg/kg).
- Fetal skeletal retardations and variations revealed an increased incidence of incomplete/delayed ossification (5th medial phalanges of digits and toes, bilateral) at the 0.1 and 1 mg/kg level.
- The lack of dose dependency of effects may be related to the formation of neutralizing anti-drug antibodies (ADAs). ADAs were observed in 4, 12, and 12 rabbits at 0.1, 0.3 and 1 mg/kg, respectively. However, TK data was not evaluated in main group animals.
- The NOAEL for maternal toxicity was the high dose (1 mg/kg); a NOAEL for fetal toxicity was not identified (<0.1 mg/kg).

Methods

Doses:	0, 0.1, 0.3, and 1 mg/kg
Frequency of dosing:	Once daily on gestation days (GD) 1, 7, and 13
Dose volume:	0.1, 0.3, and 1 mL/kg of a 1 mg/mL solution to achieve doses of 0.1, 0.3, and 1 mg/kg, respectively 1 mL/kg vehicle
Route of administration:	Subcutaneous injection
Formulation/Vehicle:	10 mM Na phosphate, 40 mM Na chloride, 0.03

	% (w/v) polysorbate-20, 5 % (w/v) sucrose (w/v), pH 6.2
Species/Strain:	Himalayan rabbits (CHBB:HM); 162-192 days old
Number/Sex/Group:	20
Satellite groups:	Three additional females per group for determination of test substance in the plasma
Study design:	One male rabbit (untreated) was mated with one female rabbit under observation. The day on which the copulation was observed was considered as day 0 of gestation. On day 29 of gestation the fetuses were delivered by cesarean section. Blood samples of all animals (before mating and sacrifice) were collected for anti-VEGF Trap antibody measurement. Plasma concentrations of free and bound VEGF Trap, and the potential formation of ADA were characterized using validated ELISA methods.
Deviation from study protocol:	None that could adversely affect interpretation of the study results

Observations and Results

Mortality (Daily)- None

Clinical Signs (Daily) – No test article-related effects

Body Weight (Daily) – Slightly lower (≤2%) body weights were observed at the high dose starting on Day 3 compared to controls. The body weight gain for the entire study period (Days 0-29) was decreased by 11.5% (not statistically significant) at the high dose compared to controls.

At the high dose, uterine weight was decreased by 13.6%. When corrected for uterine weight, there was no decrease in maternal body weight. The sponsor concluded that absolute body weight gain during gestation and corrected body weight gain were unaffected by treatment at dose levels up to 1 mg/kg. This reviewer concurs.

Feed Consumption (3 days intervals) – There were no test article-related effects on food consumption.

Toxicokinetics (Satellite group; GD 1 and 13; 0-144 hrs after the 1st injection and 0-168 hrs after the 3rd SC injection) - Except at the low dose, the majority of the total drug levels (free VEGF Trap + adjusted bound VEGF Trap) was in the free form directly after dose administration and in the bound form at the later time points. At the low dose, free VEGF Trap was detected only in 2 of the 3 rabbits during GD 2-5 and/or GD 14-16, whereas bound VEGF trap was detected from GD2 to GD 16 in all 3 rabbits. Two rabbits at 0.3 mg/kg had undetectable levels of free or bound VEGF Trap within 24-hrs after the 3rd SC injection. The 3rd rabbit had no detectable levels of free or bound VEGF Trap after GD 7. One rabbit at 1 mg/kg had undetectable levels of free or bound VEGF Trap after GD 7 (except for detectable levels only at 24 hrs after the 3rd SC injection. This high–dose rabbit showed an immunogenic response (see below). The other 2 high-dose rabbits had detectable levels of free and bound VEGF Trap up to GD 19.

Mean TK Parameters for Free VEGF Trap

Parameter	(Units)	Dose #	Group 6: 0.1 mg/kg VEGF Trap SC		Group 7: 0.3 mg/kg VEGF Trap SC		Group 8: 1 mg/kg VEGF Trap SC	
			mean	SD	mean	SD	mean	SD
t_{max}	(h)	1	36.0	17.0	24.0	0.000	24.0	0.000
		3	24.0	0.000	15.0	12.7	18.0	10.4
C_{max}	(µg/mL)	1	0.326	0.0771	0.875	0.0848	3.52	0.161
		3	0.259	0.0898	0.235	0.0912	3.87	4.03
C_{max}/Dose	(µg/mL)/ (mg/kg)	1	3.26	0.771	2.92	0.283	3.52	0.161
		3	2.59	0.898	0.782	0.304	3.87	4.03
AUC_{0-t} †	(h*µg/mL)	1	17.5	9.24	77.3	16.7	278	27.7
		3	11.3	10.2	5.62	2.89	194	194
AUC_{0-t} /Dose†	(h*µg/mL)/ (mg/kg)	1	175	92.4	258	55.7	278	27.7
		3	113	102	18.7	9.64	194	194

†t = 144h for the 1st injection, t = 168h for the 3rd injection

Mean TK Parameters for Adjusted Bound VEGF Trap

Parameter	(Units)	Dose #	Group 6: 0.1 mg/kg VEGF Trap SC		Group 7: 0.3 mg/kg VEGF Trap SC		Group 8: 1 mg/kg VEGF Trap SC	
			mean	SD	mean	SD	mean	SD
t_{max}	(h)	1	104	27.7	128	13.9	136	13.9
		3	16.0	27.7	0.000	0.000	3.00	4.24
C_{max}	(µg/mL)	1	0.244	0.0875	0.664	0.158	1.45	0.0231
		3	0.227	0.164	0.188	0.0651	2.15	1.03
C_{max}/Dose	(µg/mL)/ (mg/kg)	1	2.44	0.875	2.21	0.526	1.45	0.0231
		3	2.27	1.64	0.627	0.217	2.15	1.03
AUC_{0-t} †	(h*µg/mL)	1	25.2	10.0	66.7	10.5	138	0.306
		3	9.91	5.84	3.46	1.46	161	112
AUC_{0-t} /Dose†	(h*µg/mL)/ (mg/kg)	1	252	100	222	34.8	138	0.306
		3	99.1	58.4	11.5	4.87	161	112

†t = 144h for the 1st injection, t = 168h for the 3rd injection

ADA (Predose and GD 20 for satellite group and GD 29 for main group) – There were no anti-VEGF Trap antibodies detected in serum samples collected from the majority of animals in the satellite group. A positive ADA response was observed in one mid-dose and one high-dose rabbit. The presence of anti-VEGF Trap antibodies appeared to affect free and bound VEGF Trap plasma levels in the high-dose rabbit, but not in the mid-dose rabbit.

A positive ADA response was observed in 28 out of 59 VEGF Trap treated rabbits in the main group on GD 29 (4, 12, and 12 rabbits in the low, mid, and high-dose groups, respectively). However, it is not known if the ADA response affected free and/or bound VEGF Trap plasma levels as TK was not evaluated in these animals. It is unclear as to the reason for the large discrepancy in the number of ADA positives in the satellite (22%) versus the main study group (47%). Of note is that the TK data in the satellite group showed lower AUC values at the mid-dose compared to the low dose after the third test article administration (Day 13). Given that a positive ADA response was associated with a reduction in exposure in the satellite group (in 1 of 2 ADA-positive animals), it cannot be ruled out that the ADAs were indeed neutralizing in ADA-positive main-study animals. As such, treatment-related effects may not show dose dependency.

Dosing Solution Analysis – As noted above, the administration volume was 0.1, 0.3, and 1 mL/kg of a 1 mg/mL solution to achieve doses of 0.1, 0.3, and 1 mg/kg, respectively. The concentration of the 1 mg/mL dosing solution ranged from 100-110% of the nominal value.

Necropsy (GD 29 for main groups; GD 20 for TK group) – Hardened fatty tissue in the abdominal cavity was observed in 1, 2, 4, and 3 females at 0, 0, 0.1, 0.3, and 1 mg/kg, respectively. The sponsor included historical data for this finding showing an incidence of 4/20. Thus, the incidence observed in this study is within that of historical controls.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.) – Although findings below showed a decreased or increased incidence compared to controls, a treatment related effect was not assumed since values were within the range of historical control data. The fetal sex distribution showed a decrease in % males compared to the concurrent control as well as historical control range. However, given the lack of a test article-related effect in other C-section parameters, the finding was considered incidental.

Incidence of C-Section Findings

Finding	0	0.1	0.3	1	Historical control [a]
Corpora lutea	8.1	8.5	9.2	7.7	7.7-8.7
Implantations	7.3	7.6	8.6	7.1	6.6-7.7
% implantations	96	85	85.3	86.6	81.6-96.0
Postimplantation loss (% of implantations)	0.3	0.9	1.3	0.9	0.3-1.4
Late resorptions (% of implantations)	0.3	0.9	1.3	0.9	0.3-1.4
# fetuses	7.1	6.6	7.4	6.1	5.2-7.3
% males (litter mean)	54.8	50.6	44.2	40.7	44.2-50.2

[a]Values represent the minimal and maximal incidence observed in studies conducted during 2007, 2008, and 2010.

Offspring (Malformations, Variations, etc.) – There was an increased incidence of some malformations (mainly cardiac ventricular septal defects with/without malformation of major vessels and skeletal malformations) at all dose levels compared to the control group. Despite the lack of a dose response, the incidence of cardiac ventricular septal defects was above the range of historical control at all doses (see table below). In this table, cardiac ventricular septal defects incidence is presented in isolation, and pooled with other malformations of the heart and major vessels. The total incidence of the number of affected fetuses with cardiovascular effects (per number of litters affected) was 4(3), 8(6), 13(9) and 5(4) at 0, 0.1, 0.3 and 1mg/kg, respectively.

In addition to the findings listed in the table below, the above incidence includes 3 additional great vessel malformations that were not included in the table; specifically a malformation in the truncus arteriosus in 1 fetus at the mid-dose, ascending aorta and pulmonary artery enlargement in 1 low dose fetus, and transposition of great vessels,

enlarged aortic arch and small pulmonary artery in 1 control fetus). Therefore, the sponsor considered the cardiovascular findings to be test article related at doses up to 1 mg/kg.

Fetal examinations for skeletal effects showed a statistically significant increased incidence of delayed ossification (5th medial phalanges of digits and toes, bilateral) at the 1 mg/kg level when expressed as the number of fetuses. Although statistical significance was lacking when the calculation was done on a litter basis, the sponsor believes that a treatment-related effect cannot be excluded as these values were above the range of historical control data.

At the 0.1 mg/kg level, a statistically significant increase in delayed ossification was observed at a single localization (5th medial phalanges of digits, right), when calculation was done on a fetal basis. The sponsor noted that a treatment related effect is not assumed in this case, because statistical significance was lacking when calculation was done on a litter basis, the finding lacked dose dependency, and the value was inside the range of historical control data. The reviewer believes that a test article effect cannot be ruled out given the similar incidence with that observed at 1 mg/kg. In addition, the reviewer used the recent historical control data, within 3 years of the study date (2007, 2008 and 2009). The incidence at 0.1 mg/kg was greater than that of the historical controls during these 3 years.

The TK data showed the formation of ADAs. It can not be determined if these ADAs affected the levels of free VEGF Trap as TK analysis was not conducted in the main group animals. Based on the satellite TK data and ADA analysis, it was shown that ADA formation was associated with reduced exposure in one of two animals that were confirmed ADA-positive. Nearly fifty percent of the main study animals were confirmed to be ADA-positive. As such, it cannot be ruled out that the ADAs were indeed neutralizing in a number of animals. Given these data, it is difficult to rule out a treatment-related effect for values that were above concurrent and historical control range, despite the lack of dose-dependency.

Incidence of Fetal Findings

Finding	0	0.1	0.3	1	Historical control (max incidence)[a]
Cardiac ventricular septal defect					
Number fetus	3	7	11	4	
Fetal %	2.1	5.6	7.4	3.4	3.6%
Number litters	3	5	8	4	
Litter %	15	26	40	21.1	16.7%
Malformation of heart & major vessels, cardiac ventricular septal defect, ascending aorta enlarged					
Number fetus	0	0	1	1	
Fetal %	0	0	0.7	0.9	0.8
Number litters	0	0	1	1	
Litter %	0	0	5	5.3	5.0
Fusion of ribs (cartilaginous part)					
Number fetus	2	1	6	0	
Fetal %	1.4	0.8	4.1	0	0
Number litters	2	1	3	0	
Litter %	10	5.3	15	0	0
Medial phalanx digit incompletely ossified-					
5th right					
Number fetus	3	12**	2	14**	
Fetal %	2.1	9.5	1.4	12.1	5.4
Number litters	3	8	2	6	
Litter %	15	42.1	10.0	31.6	27.8
5^{th} left					
Number fetus	3	11	3	14**	
Fetal %	2.1	8.7	2.1	12.1	7.1
Number litters	3	7	3	6	
Litter (%)	15	36.8	15	31.6	33.3
Medial phalanx toes incompletely ossified					
5th right					
Number fetus	0	4	1	9**	
Fetal %	0	3.2	0.7	7.8	1.0
Number litters	0	4	1	4	
Litter %	0	21.1	5	21.1	5.6
5^{th} left					
Number fetus	0	4	0	7*	
Fetal %	0	3.2	0	6	0.8
Number litters	0	4	0	4	
Litter %	0	21.1	0	21.1	5.6

[a]Maximal incidence in control group in studies conducted during 2007, 2008, and 2010.
*p<0.05; **p<0.01

In addition to the malformations contained in the above table, the sponsor considered that the finding of 2 fetuses (in two litters) with spina bifida at the 0.1 mg/kg level was remarkable because this finding spontaneously occurs at a very

rare incidence in the rabbit strain used, and that historically the performing lab had never observed two affected fetuses in a single study. One of these fetuses with spina bifida additionally had gastroschisis ("abdominal hernia") with protruding organs (stomach, liver and intestines), cardiac ventricular septal defects and multiple skeletal malformations (rudimentary sternum, all ribs extremely shortened, 13^{th} to 14^{th} caudal vertebral bodies fused). The second fetus with spina bifida had delayed ossification at the 5th medial phalanges of digits and toes (bilateral) and supernumerary sternal ossification centers. Encephalomeningocele was noted in one fetus at 1 mg/kg which also showed cardiac ventricular septal defects, delayed ossification at the 5th medial phalanges of digits and toes (bilateral), and supernumerary sternal ossification centers.

Conclusion:

The following NOAELs were determined:

- Maternal toxicity: 1 mg/kg; Free VEGF Trap AUC = 278 µg•hr/mL; C_{max} = 3.52 µg/mL
- Fetal toxicity: < 0.1 mg/kg; Free VEGF Trap AUC = 17.5 µg•hr/mL; C_{max} = 0.326 µg/mL

The human mean AUC after an ITV dose of 2 mg every 4 weeks was 2.856 µg•hr/mL; the mean C_{max} was 0.0193 µg/mL (Study # VGFT-OD-0702-PK).

The calculation for exposure margin based on C_{max} was 0.326 µg/mL divided by 0.0193 mg/L = 16.89. The sponsor indicated that the cumulative AUC in rabbits was calculated as:

$AUC_{cum} = AUC1_{(0\text{-}168)} + AUC2_{(0\text{-}168)}* + AUC3_{(0.\text{-}168)}$
With $AUC2_{(0\text{-}168)} = (AUC1_{(0\text{-}168)} + AUC3_{(0\text{-}168))}/2$

According to the sponsor, the cumulative AUC in the rabbit was 28.8 µg•hr/mL. This is the sum of the AUC after the 1^{st} administration (AUC1) and the AUC after the 3^{rd} administration (AUC3), i.e, 17.5 + 11.3 (see TK table above), which is not consistent with the formula given above. The reviewer considers this is a more conservative approach as the AUC after the 2^{nd} administration (AUC2) was not determined in the plasma samples and the AUC_{cum} would be higher if the estimated AUC2 was added (providing a higher safety margin). Therefore, the exposure margin for the 2 mg clinical dose based on the 0.1 mg/kg rabbit dose is estimated to be 10.08 (i.e., 28.6/2.856). However, it should be noted that 0.1mg/kg was the lowest dose assessed and produced severe malformations. As such, there is no fetal NOAEL, and the exposure margin represents the margin over the LOAEL. No margin of safety can be presumed based on these data.

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/s/

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03/28/2013

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04/01/2013