CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125387Orig1s053

Trade Name:	EYLEA
Generic or Proper Name:	Aflibercept
Sponsor:	Regeneron Inc.
Approval Date:	October 28, 2016
Indication:	EYLEA is indicated for the treatment of patients with: ● Neovascular (Wet) Age-Related Macular Degeneration (AMD) ● Macular Edema Following Retinal Vein Occlusion (RVO) ● Diabetic Macular Edema (DME) ● Diabetic Retinopathy (DR) in Patients with DME

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125387/S-053

SUPPLEMENT APPROVAL

Regeneron Pharmaceuticals, Inc.
Attention: Candace Drumma, MS
Manager. CMC Regulatory Affairs
81 Columbia Turnpike, Bldg. 85
Rensselaer, NY 12144

Dear Ms. Drumma:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received June 30, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for EYLEA (aflibercept) Injection.

This Prior Approval supplemental biologics application provides for the replacement of the filter needle with (b) (4) "vial adapter" inside the EYLEA vial carton.

APPROVAL & LABELING

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text, which is identical to the labeling submitted on October 25, 2016.

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.

CARTON LABEL

Submit the final printed carton label that is identical to the enclosed carton label, as soon as it is available, but no more than 30 days after it is printed. Please submit the label electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton Label for approved BLA 125387/S-053**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of these criteria apply to your application, this requirement is not applicable.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug

Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, call 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
Office of New Drugs
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
10/28/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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

- Dosage and Administration, Neovascular (Wet) Age-Related Macular Degeneration (AMD) (2.2) 5/2016
- Dosage and Administration, Diabetic Macular Edema (DME) (2.4) 5/2016
- Dosage and Administration, Diabetic Retinopathy (DR) in Patients with DME (2.5) 5/2016
- Contraindications, Hypersensitivity (4.3) 10/2016
- Dosage and Administration, Preparation for Administration (2.6) 10/2016
- Dosage and Administration, Injection Procedure (2.7) 10/2016

INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy (DR) in Patients with DME (1.4)

DOSAGE AND ADMINISTRATION

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 in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). (2.2)

Macular Edema Following Retinal Vein Occlusion (RVO)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly). (2.3)

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with Diabetic Macular Edema

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.4, 2.5)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months). (2.4, 2.5)

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 floaters, intraocular pressure increased, and vitreous detachment. (6.1)

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: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

***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:

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

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR) in Patients with DME

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions

For ophthalmic intravitreal injection. 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 in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.1)*]. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)

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), (14.3)*].

2.4 Diabetic Macular Edema (DME)

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 5 injections, 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 in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.4)*]. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.5 Diabetic Retinopathy (DR) in Patients with DME

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 5 injections, 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 in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.5)*]. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.6 Preparation for Administration

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

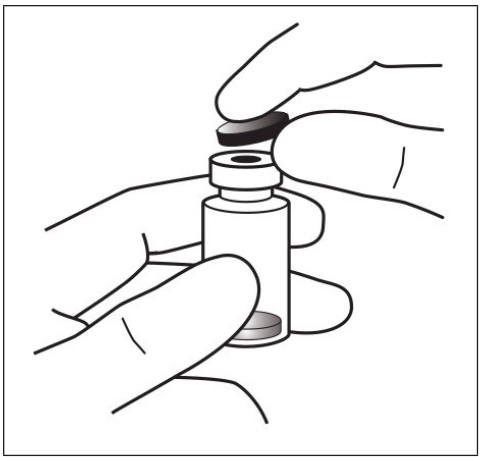
Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle.

Vial and Vial Adapter with 5-micron filter

The glass vial and vial adapter are for single use only.

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

Figure 1:

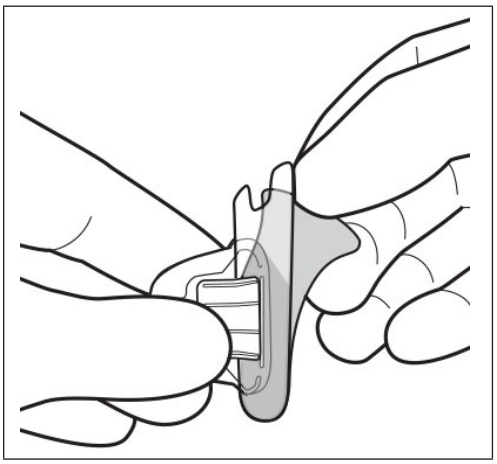


2. Using aseptic technique, clean the top of the vial with an alcohol wipe (see Figure 2).

Figure 2:

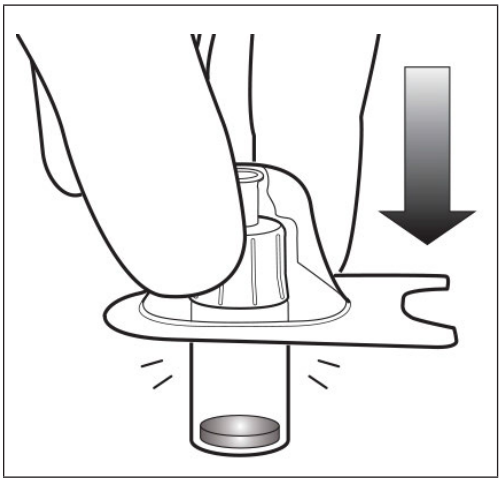
3. Remove the protective seal from the vial-adapter package. Do not remove the sterilized vial adapter from the package. The vial adapter will remain in the package and will not fall out (see Figure 3).

Figure 3:



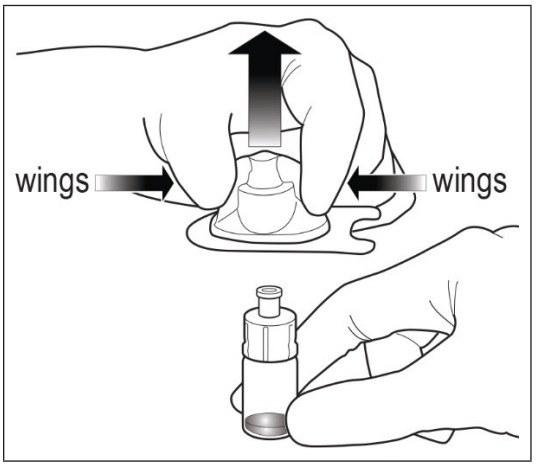
4. Grasp the vial-adapter cover and push the adapter spike into the rubber stopper until the adapter is firmly attached to the vial. You may hear a click (see Figure 4).

Figure 4:



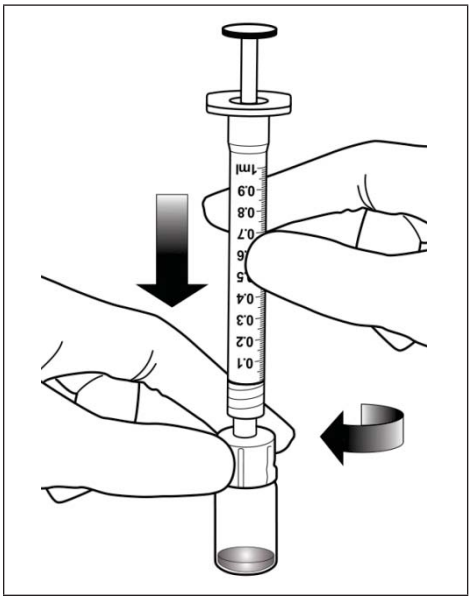
5. Squeeze the “wings” on the vial-adapter package as shown and remove by pulling upward (see Figure 5).

Figure 5:



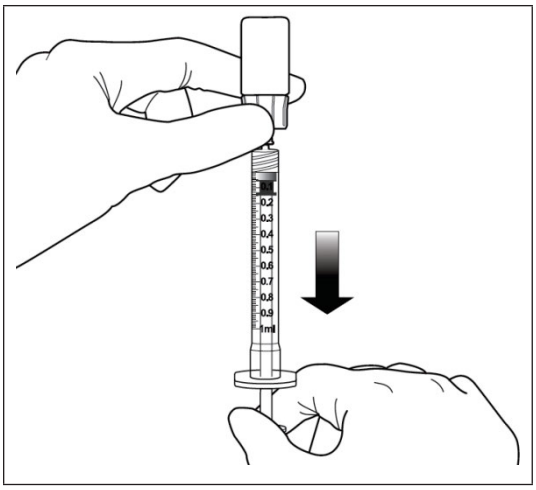
6. While securely holding the vial adapter, attach the syringe by twisting it onto the Luer lock (see Figure 6).

Figure 6:



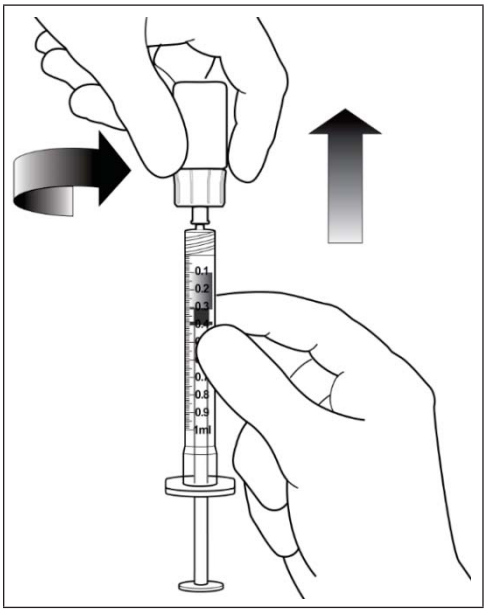
7. Invert the vial with syringe and vial adapter attached. Using aseptic technique slowly withdraw all of the EYLEA vial contents into the syringe (see Figure 7).

Figure 7:



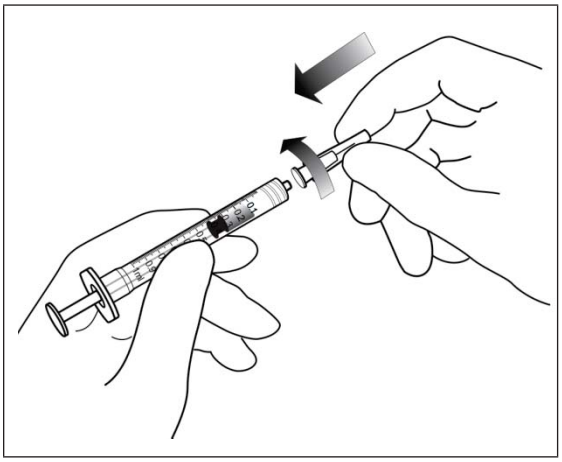
8. While holding the vial adapter, remove the syringe by twisting the adapter (see Figure 8).

Figure 8:



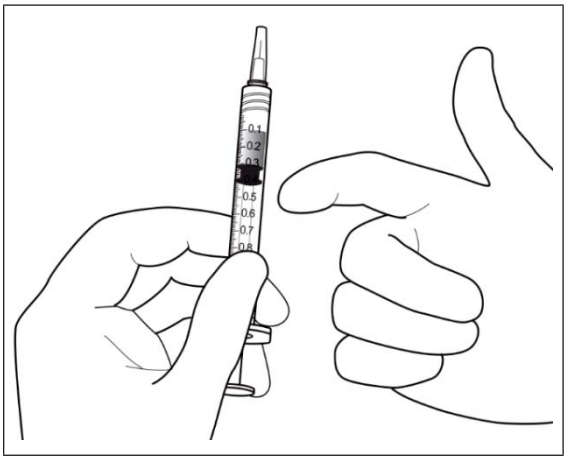
9. Remove the 30-gauge x ½-inch injection needle from the sterile container and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 9).

Figure 9:



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 10).

Figure 10:



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 11a and 11b).

Figure 11a:

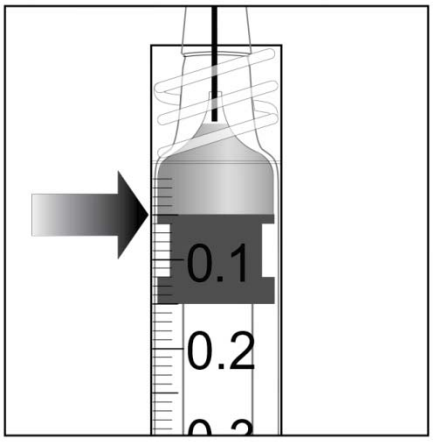
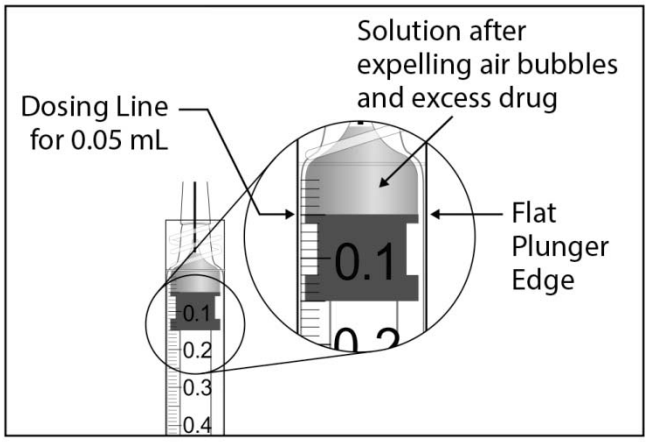


Figure 11b:



2.7 Injection Procedure

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, vial adapter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) 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 rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or 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 (2.7) 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 vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.7)*].

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 of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials 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 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

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%
Ocular hyperemia	4%	8%
Corneal epithelium defect	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 hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO)

The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT) [*see Clinical Studies (14.2), (14.3)*].

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

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

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

Diabetic Macular Edema (DME)

The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100 [*see Clinical Studies (14.4)*].

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival	28%	17%	31%	21%

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
hemorrhage				
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 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, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. 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.

Females of reproductive potential should use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

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 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) 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 Retinal Vein Occlusion (RVO)

Reductions in mean retinal thickness were observed in COPERNICUS, GALILEO, and VIBRANT at week 24 compared to baseline. Anatomic data were not used to influence treatment decisions [*see Clinical Studies (14.2), (14.3)*].

Diabetic Macular Edema (DME)

Reductions in mean retinal thickness were observed in VIVID and VISTA at weeks 52 and 100 compared to baseline. Anatomic data were not used to influence EYLEA treatment decisions [*see Clinical Studies (14.4)*].

12.3 Pharmacokinetics

EYLEA is administered intravitreally to exert local effects in the eye. In patients with wet AMD, RVO, or DME, 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, RVO, and DME, the mean C_{max} of free aflibercept in the plasma was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL), 0.05 mcg/mL (range: 0 to 0.081 mcg/mL), and 0.03 mcg/mL (range: 0 to 0.076 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 RVO study and in patients in a DME study. No dose adjustment based on renal impairment status is needed for either wet AMD, RVO, or DME patients.

Other

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

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 4 and Figure 8 below.

Table 4: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies

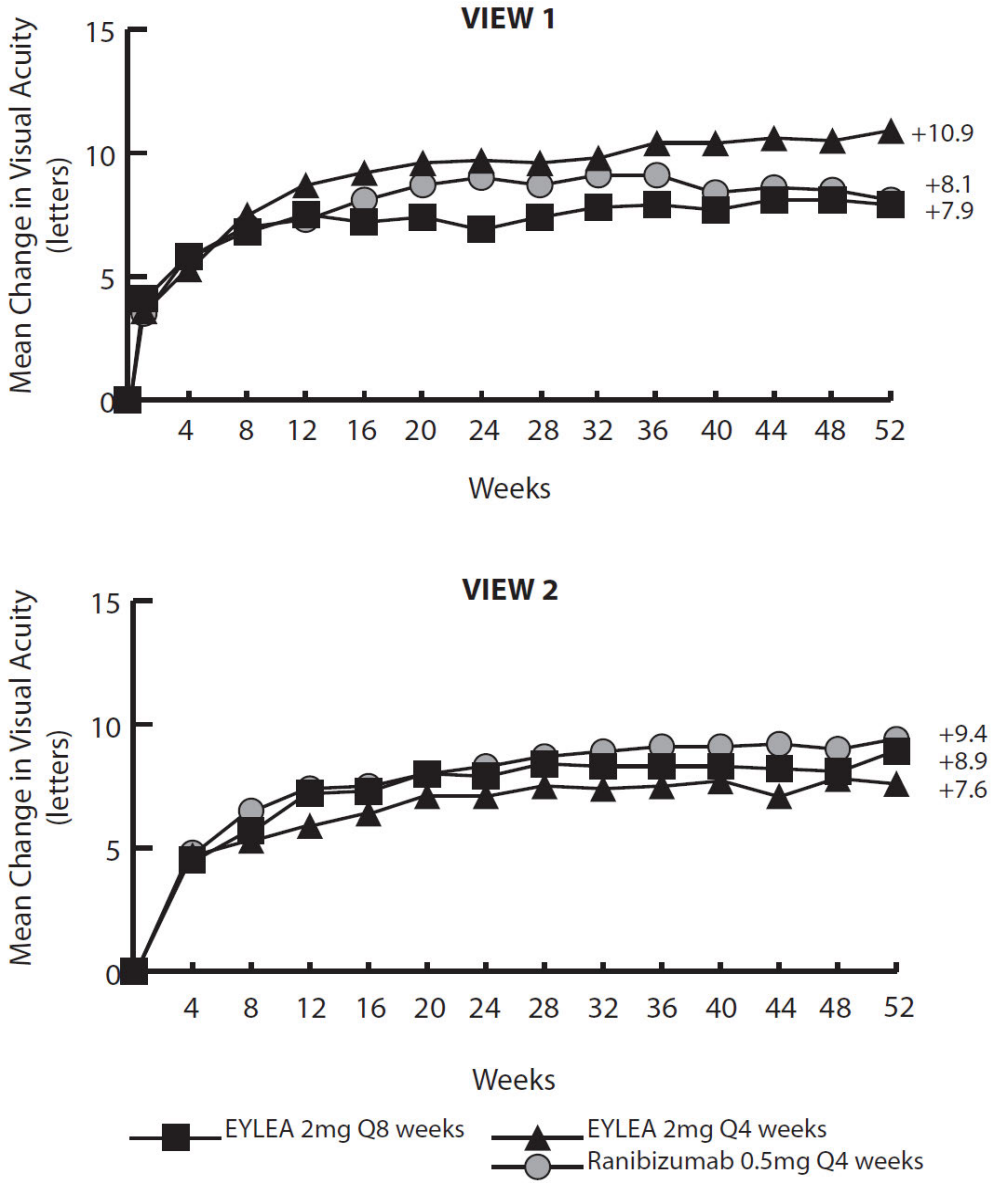
	VIEW1			VIEW2		
	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
Efficacy Outcomes						
Proportion of patients who maintained visual acuity (%) (<15 letters 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.

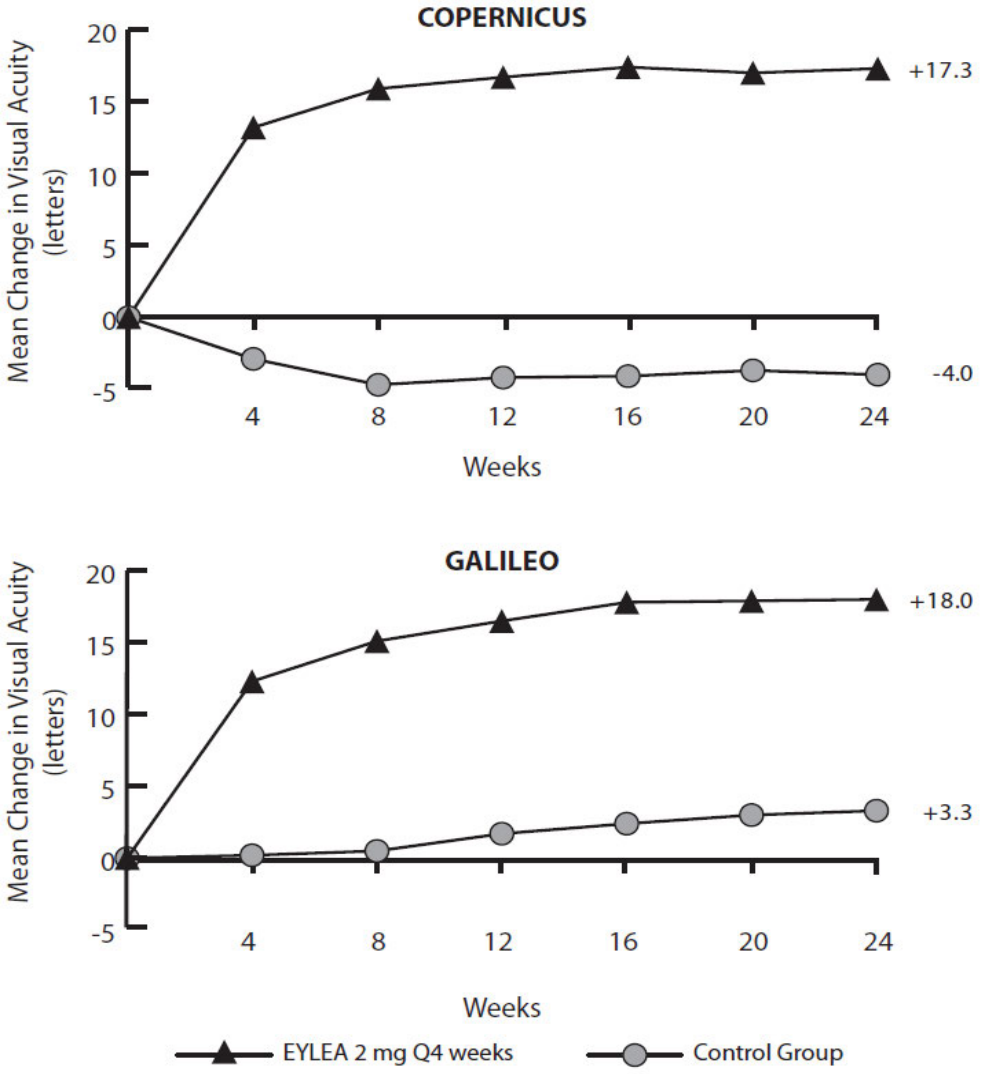
Results from the analysis of the COPERNICUS and GALILEO studies are shown in Table 5 and Figure 9 below.

Table 5: 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.

14.3 Macular Edema Following Branch Retinal Vein Occlusion (BRVO)

The safety and efficacy of EYLEA were assessed in a 24-week, randomized, multi-center, double-masked, controlled study in patients with macular edema following BRVO. A total of 181 patients were treated and evaluable for efficacy (91 with EYLEA) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4) or laser photocoagulation administered at baseline and subsequently as needed (control group). Patient ages ranged from 42 to 94 years with a mean of 65 years.

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

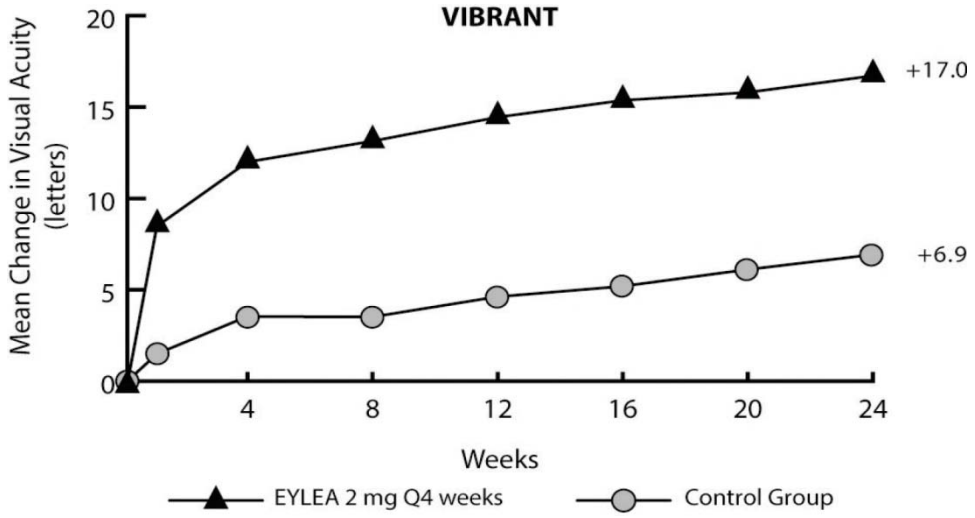
Detailed results from the analysis of the VIBRANT study are shown in Table 6 and Figure 10 below.

Table 6: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in VIBRANT Study

	VIBRANT	
	Control	EYLEA 2 mg Q4 weeks
	N=90	N=91
Efficacy Outcomes		
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	26.7%	52.7%
Weighted Difference [a,b] (%) (95% CI)		26.6%[c] (13.0, 40.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	6.9 (12.9)	17.0 (11.9)
Difference in LS mean [a,d] (95% CI)		10.5[c] (7.1, 14.0)

[a] Difference is EYLEA 2 mg Q4 weeks minus Control
[b] Difference and CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (> 20/200 and ≤ 20/200)
[c] $p<0.01$ compared with Control
[d] LS mean and CI based on an ANCOVA model

Figure 10: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in VIBRANT Study



Treatment effects in evaluable subgroups (e.g., age, gender, and baseline retinal perfusion status) in the study were in general consistent with the results in the overall populations.

14.4 Diabetic Macular Edema (DME)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Patient ages ranged from 23 to 87 years with a mean of 63 years.

Of those, 576 were randomized to EYLEA groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 5 initial monthly injections (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the EYLEA groups could receive laser and patients in the laser group could receive EYLEA.

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score. Efficacy of both EYLEA 2Q8 and EYLEA 2Q4 groups was statistically superior to the control group. This statistically superior improvement in BCVA was maintained at week 100 in both studies.

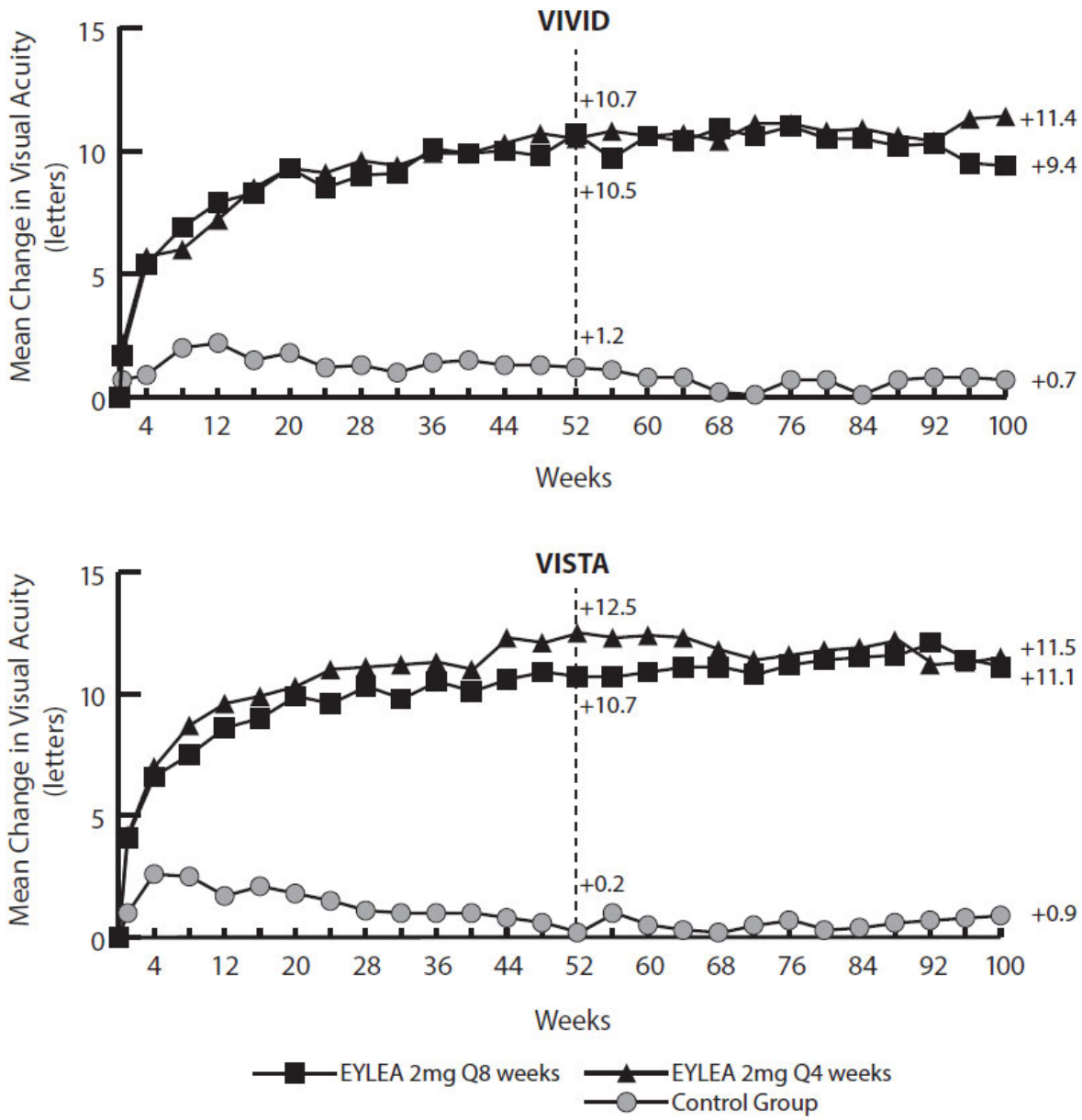
Results from the analysis of the VIVID and VISTA studies are shown in Table 7 and Figure 11 below.

Table 7: Efficacy Outcomes at Weeks 52 and 100 (Full Analysis Set with LOCF) in VIVID and VISTA Studies

	VIVID			VISTA		
	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	Control
Full Analysis Set	N=135	N=136	N=132	N=151	N=154	N=154
Efficacy Outcomes at Week 52						
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	10.7 (9.3)	10.5 (9.6)	1.2 (10.6)	10.7 (8.2)	12.5 (9.5)	0.2 (12.5)
Difference[b, c] in LS mean (97.5% CI)	9.1[d] (6.3, 11.8)	9.3[d] (6.5, 12.0)		10.5[d] (7.7, 13.2)	12.2[d] (9.4, 15.0)	
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	33.3%	32.4%	9.1%	31.1%	41.6%	7.8%
Adjusted Difference[c, e] (%) (97.5% CI)	24.2%[d] (13.5, 34.9)	23.3%[d] (12.6, 33.9)		23.3%[d] (13.5, 33.1)	34.2%[d] (24.1, 44.4)	
Efficacy Outcomes at Week 100						
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	9.4 (10.5)	11.4 (11.2)	0.7 (11.8)	11.1 (10.7)	11.5 (13.8)	0.9 (13.9)
Difference[b, c] in LS mean (97.5% CI)	8.2[d] (5.2, 11.3)	10.7[d] (7.6, 13.8)		10.1[d] (7.0, 13.3)	10.6[d] (7.1, 14.2)	
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	31.1%	38.2%	12.1%	33.1%	38.3%	13.0%
Adjusted Difference[c, e] (%) (97.5% CI)	19.0%[d] (8.0, 29.9)	26.1%[d] (14.8, 37.5)		20.1%[d] (9.6, 30.6)	25.8%[d] (15.1, 36.6)	

[a] After treatment initiation with 5 monthly injections
[b] LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, protocol specified stratification factors were included in the model.
[c] Difference is EYLEA group minus Control group
[d] $p<0.01$ compared with Control
[e] Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors.

Figure 11: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 100 in VIVID and VISTA Studies



Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor prior to study participation were similar to those seen in patients who were VEGF inhibitor naïve prior to study participation.

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity, prior anti-VEGF therapy) in each study were in general consistent with the results in the overall populations.

14.5 Diabetic Retinopathy (DR) in Patients with DME

In the VIVID and VISTA studies, an efficacy outcome was the change in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (ETDRS-DRSS). The ETDRS-DRSS score was assessed at baseline and approximately every 6 months thereafter for the duration of the studies [*see Clinical Studies (14.4)*].

All enrolled patients had DR and DME at baseline. The majority of patients enrolled in these studies (77%) had moderate-to-severe nonproliferative diabetic retinopathy (NPDR) based on the ETDRS-DRSS. At week 100, the proportion of patients improving by at least 2 steps on the ETDRS-DRSS was significantly greater in both EYLEA treatment groups (2Q4 and 2Q8) when compared to the control group.

Results from the analysis of ETDRS-DRSS at week 100 in the VIVID and VISTA studies are shown in Table 8 below.

Table 8: Proportion of Patients who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score at Week 100 (LOCF[a]) in VIVID and VISTA Studies

	VIVID			VISTA		
	EYLEA 2 mg Q8 weeks [b]	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q8 weeks [b]	EYLEA 2 mg Q4 weeks	Control
Evaluable Patients[c]	N=101	N=97	N=99	N=148	N=153	N=150
Number of patients with a ≥2-step improvement on ETDRS-DRSS from Baseline (%)	32 (32%)	27 (28%)	7 (7%)	56 (38%)	58 (38%)	24 (16%)
Difference[d,e](%) (97.5% CI)	24%[f] (12, 36)	21%[f] (9, 33)		22%[f] (11, 33)	22%[f] (11, 33)	

[a] Non-gradable post-baseline ETDRS-DRSS values were treated as missing and were imputed using the last gradable ETDRS-DRSS values (including baseline values if all post-baseline values were missing or non-gradable)
[b] After treatment initiation with 5 monthly injections
[c] The number of evaluable patients included all patients who had valid ETDRS-DRSS data at baseline
[d] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors
[e] Difference is EYLEA minus Control group
[f] $p<0.01$ compared with Control

Results of the evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity) on the proportion of patients who achieved a ≥2-step improvement on the ETDRS-DRSS from baseline to week 100 were, in general, consistent with those in the overall population.

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 (2.6) and (2.7)*].

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 single-use vial adapter with 5-micron filter 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 patients 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: XX October 2016

Initial U.S. Approval: 2011


Black
Pantone 302
Pantone 2728
NDC 61755-005-02
EYLEA®
(aflibercept) Injection
For Intravitreal Injection
2 mg/0.05 mL
Single-use Vial
Carton contents: Each EYLEA carton contains
• one single-use, 3-mL, glass vial of EYLEA
• one single-use vial adapter with 5-micron filter for withdrawal of the vial contents
• one 30-gauge x ½-inch needle for intravitreal injection
• one 1-mL plastic syringe for administration
• one package insert
℞ ONLY
Vial contents: Each EYLEA single-use vial is designed to deliver 0.05 mL (50 microliters) of EYLEA (40 mg/mL) aqueous solution with 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2.
Dosage and Administration:
See package insert for dosage information and directions for use.
Store refrigerated at 2–8°C (36–46°F).
Do not freeze. Protect from light.
No U.S. standard of potency.
U.S. License No. 1760
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Origin U.S.
EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.
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Manufactured by Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road, Tarrytown, NY 10591
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s053

MEDICAL REVIEW(S)

Clinical Review of BLA 125387
Supplement 053

BLA 125387/S-053

SDN-526	Submission Date: 6/30/16 Received Date: 6/30/16
SDN-528	Submission Date: 7/1/16 Received Date: 7/1/16
SDN-543	Submission Date: 8/31/16 Received Date: 8/31/16
	Review Date: 9/23/16
Applicant:	Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591-6707 914-345-7926
Applicant's Representative:	Candace Drumma Manager, CMC Regulatory Affairs
Drug:	Eylea (aflibercept) Injection
Pharmacologic Category:	anti-VEGF

Submitted:
Through this supplement, Regeneron is seeking approval from the Agency to replace the current filter needle with [redacted] (b) (4) "vial adapter" inside the Eylea vial carton. The vial adapter will be used to transfer liquid drug product from the primary container (vial) into the delivery syringe. This operation is currently carried out with the filter needle.

Labeling
Included in this submission are the updated proposed labeling of the Eylea carton and the USPI for the replacement of the current filter needle with the [redacted] (b) (4) vial adapter.

Compatibility
Per the applicant, the [redacted] (b) (4) vial adapter introduces no new product contact materials into the Eylea dose preparation procedure. The vial adapter is constructed from the same medical grade material as the filter needle that is provided in the currently marketed carton. The filter needle will be replaced with the [redacted] (b) (4) vial adapter while all other components inside the Eylea carton will remain the same. Per the applicant, testing has demonstrated that Eylea drug solution is compatible with the [redacted] (b) (4) vial adaptor and

that the stability of doses prepared are comparable to doses prepared using the currently used BD filter needle.

Preparation of More Than One Dose from a Single Vial Using the Vial Adapter
In reference to the Agency's Information Request to Regeneron, dated December 7, 2012, a feasibility study was conducted demonstrating that it is not possible to prepare more than one dose of Eylea from a single vial when using the [redacted] (b) (4) vial adapter during dose preparation.

Human Factors Validation Labeling Comprehension Study
Reference is made to the [redacted] (b) (4) and reference is also made to the Draft Labeling Comprehension Study Protocol [redacted] (b) (4) Per the applicant, the findings from this study support that the intended users of this product can successfully prepare doses using the proposed labeling.

RGN-2015-Andromeda-ST-503: "**Human Factors Validation Labeling Comprehension Study: EYLEA® (aflibercept) Injection Vial and Vial Adapter"**

This study included a total of 33 participants (17 = retinal specialists, 16 = health care professionals) to perform tasks and answer questions associated with the comprehension of the vial and vial adapter carton, labeling, and Package Insert. The study consisted of 45-minute long, one-on-one sessions. Observational data and subjective evaluations from the participants were collected.

The intended user population for the vial and vial adapter are retinal specialists and health care providers. Retinal specialists have advanced ophthalmic training, specialize in vitreoretinal/retinal diseases, and have experience preparing doses and always administering intravitreal injections. Health care providers include ophthalmic technicians and nurses that work with retinal specialists to prepare syringes for intravitreal injections but do not administer intravitreal injections.

Device Training and Training for Study Participation
Each participant received Eylea Vial and Vial adapter carton packaged with written and illustrated instructions, in the form of a Package Insert. Participants were provided an opportunity, but not required, to familiarize themselves with these materials prior to starting the tasks if they felt it was needed. Moreover, though not required, participants were also allowed to reference the Package Insert while completing the tasks and answering the labeling comprehensions questions. No additional training was provided to the participants.

Study Materials
A variety of materials were used in the study. They included:

- EYLEA carton & contents (vial, vial adapter, syringe, needle, Package Insert)

- Informed Consent (paper)
- Sunshine Act Form (paper)
- Interview Guide (paper) - used to capture the participant's performance and responses by moderator and note taker
- Data spreadsheet (electronic) - Interview Guide responses entered to allow for data analysis
- Desks
- Chairs
- Alcohol sanitizer
- Alcohol pads
- Gloves
- Masks
- Sharps container
- Wastebasket
- Magnifying glass

Session Outline

The testing sessions followed a standard one-on-one protocol in which a moderator conducted each session with only one participant at a time. Each session lasted up to 45 minutes.

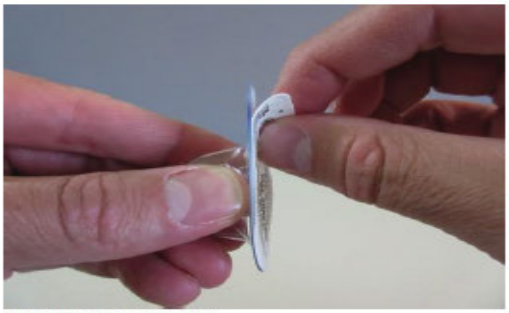
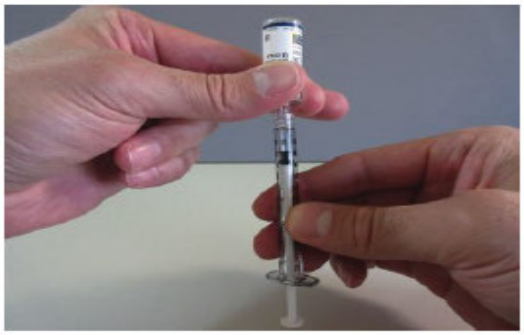
Table 4. Study Workflow

Step	Description	Duration
1. Complete Informed Consent and Sunshine Act Form	Upon arrival at the research facility, participants were instructed to read and sign the Informed Consent (Appendix 10.1) by a staff member.	10 min
2. Study Introduction	Prior to starting the tasks, the moderator read a standardized script to ensure consistent study introduction across all participants. Then the moderator asked the participant to complete a set of background questions.	5 min
3. Labeling Familiarization	After reading the script and completing the background questions, participants were provided an opportunity to familiarize themselves with the carton contents. Specifically, they were allowed to take the contents out, open and review the Package Insert, but not open any of the sealed or sterile items (i.e., vial, vial adapter, syringe, and needle).	5 min
4. Syringe Preparation Tasks	When the participants indicated that he/she was ready to start the session, the moderator instructed the participants that "A patient has just arrived at your office to receive an intravitreal injection. Perform all steps necessary to prepare the syringe." The moderator recorded the participant's performance and comments made for each of the five subtasks on the Interview Guide (Appendix	10 min

	10.4). If participants experienced any use errors, close calls, or operational difficulties and did not consult the Package Insert while completing the task, the moderator asked the participant to complete it a second time, while consulting the instructions for use step-by-step. The participants were provided gloves and masks, but were not required to wear them during the study. Also, they were allowed access to a magnifying glass if they needed it to read the print or clearly see the images on the Package Insert.	
5. Labeling Comprehension Questions	After completing the Syringe Preparation Tasks, participants were asked ten questions to assess labeling comprehension. They were instructed, "You can refer to the carton and package insert to answer all of the questions."	5 min
6. Follow Up Questions	Participants were asked three additional questions: • Do you have any additional feedback on this material? • Is there anything you think could be improved? • Do you have experience using vial adapters?	5 min
7. Remuneration	After the Follow Up Questions were answered, the physicians completed the Sunshine Act Form (Appendix 10.2) and the ophthalmic technicians and nurses completed the Healthcare Professional Background Form (Appendix 10.3). Afterwards, the participant was walked to the front where the research facility staff paid the participant in cash or check. Retinal specialists were paid $500 and health care providers $250 for their participation.	5 min

Reviewer's Comments: *Acceptable.*

Table 5. Visual Workflow of Syringe Preparation Tasks

 Clean the top of the vial with an alcohol wipe	 Remove protective seal
 Push vial adapter spike into the rubber stopper on top of the vial until it locks into place	 Squeeze the wings on vial adapter cover to remove it
 Attach syringe to vial adapter	 Invert vial and draw all vial contents into syringe
 Detach syringe from vial	Note: participants did not attach an administration needle.

Data Collection Methods

Objective Performance Scoring
During task completion, participant task performance was classified into one of five categories:
(1) okay - successful performance of the task
(2) operational difficulty - able to successfully perform the task after initial challenges;
(3) close call - almost committed a use error but was able to self-correct without moderator input
(4) use error - failure to complete the task or failure to complete the task correctly; or
(5) re-direct to instructions - instructed by the moderator to re-review the package insert.
Note: participants did not attach an administration needle.

A root cause analysis was performed for any subtask that didn't receive an "okay." A follow-up risk analysis will be conducted to evaluate the close calls and operational difficulties observed during the testing to determine if modifying the design and/or instructions could mitigate them.

Detection of Unanticipated Use Issues
In addition to monitoring participant performance for evidence of use-related hazards, participant actions and behaviors were monitored for unanticipated use issues. This included any outward signs of confusion (ie. tensed facial expressions, head scratching, long pauses between steps, etc.) as well as spontaneous comments made by participants during the simulation.

Non-Simulation Assessment Methods
Some aspects of device use may not be effectively evaluated through observation of performance during simulated use. Thus, questions were posed to gauge labeling comprehension in order to evaluate whether participants understood the device labeling information as it pertains to preparing an injection. Questions were scored in real time by the moderator to allow for follow up discussion for incorrect answers.

Reviewer's Comments: *Acceptable.*

Table 6. Labeling Comprehension Questions and Answers

#	Question	Correct Answer
1.	What does the carton contain?	Vial adapter Vial of active drug Injection needle Syringe Instructions for use / Package Insert
2.	Where should you store the carton?	Refrigerator
3.	What is the expiration date and lot #?	Correctly identifies Expiration Date and LOT #
4.	How do you remove the protective seal from the vial adapter package?	While holding the vial adapter package with one hand, grasp the seal at the finger reveal area with the other hand and pull it away from the package.
5.	True or False: After you wash your hands, you must carefully remove the vial adapter from its plastic holder with your finger tips and snap it onto the vial.	False
6.	Is it necessary to remove the vial adapter from the plastic holder to attach the vial adapter to the vial?	No
7.	How are you supposed to get the vial adapter out of the plastic holder after peeling off the seal?	Attach it to the vial
8.	How do you know that the vial adapter is firmly attached to the vial?	An audible click may be heard / Cannot push any further
9.	How do you remove the vial adapter cover off the vial?	Squeeze it and it releases
10.	In what position do you hold the vial with syringe to withdraw all the contents into the syringe?	Invert the vial with the syringe

Analysis and Interpretation of Results

The analysis included a review of task performance, participant comments, and participant responses to questions posed during the post-session interview. When issues were observed (ie. use errors, close calls, operational difficulties, unanticipated problems, or concerns raised by study participants), the analysis sought to identify the root causes of these issues. Both the moderator's observations of performance issues, and the participant's subjective feedback regarding task difficulties were considered. The analysis sought to determine whether observed issues were attributable to the design of the device, the Package Insert, or other presentation materials.

Summary of Participant Performance on Preparing Syringes Tasks

Table 7. Task Performance - Prepare Syringes with Instructions

	Okay	OD	Operational Difficulty	CC	Close Call	UE	Use Error

Participant	1. Remove protective seal and push vial-adapter spike into the rubber stopper on top of the vial until it locks into place	2. Squeeze the wings on vial-adapter cover to remove it	3. Attach syringe to vial adapter	4. Insert vial and draw all vial contents into syringe	5. Detach syringe from vial
Retinal Specialists					
(b) (6)		CC			
	OD				
	OD				
		OD			

(b) (6)					

Participant	1. Remove protective seal and push vial-adapter spike into the rubber stopper on top of the vial until it locks into place	2. Squeeze the wings on vial-adapter cover to remove it	3. Attach syringe to vial adapter	4. Insert vial and draw all vial contents into syringe	5. Detach syringe from vial
Health Care Professionals (including Ophthalmic Technicians and Nurses)					
(b) (6)					
		OD			
		CC			
	UE				
		OD			
	UE				
		OD			
	OD	UE			
		OD			

(b) (6)					
		UE			

Review of Use-Related Issues on Preparing Syringes Tasks

The following section provides detailed information regarding the specific use errors, close calls, and operational difficulties that were observed during the study (also provided in Table 5).

Remove protective seal and push vial-adapter spike into the rubber stopper on the top of the vial until it locks into place (Task 1).

Participant (b) (6) & (b) (6) – Removed vial adapter from packaging with fingers (Use Issue)

Summary

Initially, both participants removed the vial adapter from its cover with their fingertips while wearing gloves. When asked to complete the task again, while following the PI steps, they were able to determine that the vial adapter should be affixed to the vial while still in the cover and that it should only be removed by squeezing the wings. They were able to successfully complete the task on the second attempt. Both participants briefly reviewed the PI ((b) (6) = 65 seconds; (b) (6) = 83 seconds) prior to starting the syringe preparation part of the study. During the post task interview (PTI), (b) (6) stated that it's "natural instinct for techs to take things out of the plastic" and "we do what's comfortable for us." He also stated that he didn't see anything in the PI, during his initial review that gave him an indication that he should pull the adapter out with his fingers. (b) (6) stated that "it was in the container and I needed to grab it out" and that he thought it was more sterile to remove with his gloved fingers rather than using the cover to affix the vial adapter to the vial. Moreover, he noted that he would be wearing sterile gloves in surgery when he would remove the vial adapter from the packaging.

Applicant's Root Cause Analysis

Both participants are ophthalmic technicians that work in clinics where eye surgeries are performed in an Operating Room, and prepare approximately 12 ((b) (6)) to 50 (b) (6)) intravitreal injections per month, although they don't have experience with EYLEA. Their point of reference appeared to be procedures done in the operating room (i.e., (b) (6) identified himself as a (b) (6) and (b) (6) as an (b) (6)) and therefore they assumed that they would be using the Vial and Vial Adapter system in a sterile OR setting while wearing sterile gloves. Moreover, the participants noted that their typical workflow is to remove several sterile items from packaging prior to a surgery. So for this task it made sense, prior to reading the instructions in the Package Insert, to follow the same procedure for this task given that the vial adapter is in a sterile enclosure.

Participants (b) (6) – Uncertainty regarding where the vial adapter fit in the delivery system (Operational Difficulty)

Summary

These three participants were initially uncertain about where the vial adapter fit within the system. All three participants were able to correctly determine the need to affix the vial adapter to the vial and they did so. (b) (6) initially thought that the syringe would fit into the vial adapter, but quickly realized that the spike had to go into the rubber stopper of the vial. (b) (6) looked over the system components, but she did not open the PI prior to attempting to prepare the syringe. She later said that if she were using this delivery system for the first time, she would play with it on her own before attempting to use it in a clinic situation. She had used vial adapters previously in the OR and she knew that it was a filter and she said that she associated filters with syringes. She quickly figured out

that the vial adapter went into the vial and she remarked that once she figured out that the vial adapter fit onto the vial, the rest of the process was clear. (b) (6) also initially thought that the syringe would fit into the vial adapter, but quickly realized that the VA spike had to go into the rubber stopper of the vial. He looked again at the PI and then placed the vial into the vial adapter. He explained that when he read that the vial adapter must stay in the packaging; this made him initially think that it should go directly onto the syringe. He also noted that in Figure 4 the vial looked as if it were the end of the syringe. Once he examined the attachment ends of the two components (ie. the vial adapter and the syringe), he realized that they would not fit together. He later explained that he "thought it through and because he knew the vial adapter had a spike, he realized that it had to go into the vial". (b) (6) initially thought he should remove the vial adapter from the packaging. He began to reach for it with his fingers and then stopped to prevent contamination of the spike. He then tried to remove the vial adapter from the packaging by squeezing the wings, as per the instructions, but was unable to because the vial adapter was not secured on the vial. He was uncertain what to do next so the moderator re-directed him to the PI. Up to this point, he had only skimmed the PI and he had not opened the vial. After reviewing the PI more thoroughly, he opened the vial and swabbed the top, and then correctly placed the vial adapter spike into the rubber stopper of the vial. During the post-task interview, he remarked that initially he was looking at the text of the PI and did not use the figures because they were not clear to him. He explained that he read the text instruction in Step 4, "Push the adapter spike into the rubber stopper," but was unsure about which rubber stopper since the instruction did not specify the rubber stopper of the vial. This may have been partly a test situation artifact. During the task simulation, he indicated an unwillingness to open the EYLEA vial, stating "you don't want me to waste this, do you? This is a really expensive medication." He only opened the vial after the moderator indicated that this was a simulation only and doing so was acceptable.

Applicant's Root Cause Analysis

There appears to be a distinct root cause for each for these users' use errors.

- (b) (6) did not read the PI and assumed that her own knowledge would be sufficient.
- (b) (6) was confused by the PI images and where to place the vial adapter. The image in Figure 4 appeared to show the vial adapter attached to the end of the syringe.
- For (b) (6), the main root cause appears to be a test artifact. This participant did not want to open the EYLEA vial and therefore tried to prepare the administration system using only the other components of the system, specifically, the vial adapter and the syringe.

Squeeze the wings on vial-adapter cover to remove it (Task 2).
Participant (b) (6) and (b) (6) – Vial adapter initially dislodged from vial when removing cover (Use Error)

Summary

Both participants did not initially understand where the "wings" were on the Vial Adapter cover and therefore struggled to remove the cover. In the course of trying to squeeze the

plastic cover in different ways, they pulled the VA cover off with the Vial Adapter still inside. (b) (6) squeezed (see Image 8) the sides of the Vial Adapter cover along the plane of the wings, but with his fingers on the rim of the plastic cover. (b) (6) squeezed (see Image 9) the two tabs on the rim of the plastic cover that are designed to allow for easy removal of the Tyvek® seal. In both cases the participants were able to squeeze in such a way that it changed the geometry of the cup that holds the vial adapter, allowing the cover to release from the vial adapter. Both immediately realized this was an error and replaced the Vial Adapter and cover on the vial without touching the VA or further exposing the spike, then found the wings and cleanly removed the cover. When asked to perform the task a second time, both participants completed it without difficulties.

Applicant's Root Cause Analysis

The root cause of this error for both participants appears to be that the images in Figures 4 and 5 did not effectively communicate the location of the "wings" described in the text of the instructions. (b) (6) stated that he was mostly using the text on the PI to guide him, rather than the images in the associated figures, but he further noted that Figures 4 and 5 were not clear and he did not understand to what the term wings referred. The participant (31 years old) did not see the words "wings" that are written below the Vial Adapter in Figure 5 until the moderator provided him with a magnifying glass. (b) (6) also indicated that the images would have communicated more effectively if they were bigger, or if there was an additional call-out image (in Figure 3, 4, or 5) of the Vial Adapter with arrows clearly indicating the wings. This participant also observed that in Figures 4 and 5 it is difficult to see how the fingers are positioned relative to the geometry of the VA cover because it is difficult to see the wings versus the fingers. "I did not see those as wings. I saw that in the text, but didn't know what it referred to." After the moderator provided a magnifying glass, she further noted "Oh now I see the arrows pointing to the wings, but I did not see them before. Even with the magnifying glass I can barely see the dotted lines. If the image were bigger it would communicate better, or add an image next to it with arrows pointing to the wings." For users who are unfamiliar with vial adapters, as these participants were, the process of squeezing the "wings" is not initially intuitive and the current PI images are not sufficiently helpful in communicating this process. However, both users noted that after using the system one time, they would be able to easily use it correctly in all subsequent uses. This view was echoed by almost every study participant.

Participant (b) (6) – Vial adapter partially dislodged from vial when removing cover (Close Call)

Summary

As the participant was attempting to remove the cover from the affixed vial adapter, it was partially dislodged from the vial. She initially attempted to remove it while holding the base of the cover perpendicular to the wings. This was done while following the PI steps. When the moderator had her complete the task again, she placed her finger in the base cutout and her thumb on the other end (a different orientation than the first time). This seemed more natural to her. She stated that "they included a finger tab to make it easier" to remove the cover. Moreover, she thought that the two "dots" on the tabs

indicated that you're supposed to grasp there to remove the cover. When asked to re-review the PI, she stated "I didn't read that part" when referring to Step 5 and at first asked "what are the wings?" before figuring it out on her own. When asked to complete the task again, she was able to successfully remove the cover from the affixed vial adapter. But, she did comment that it was easier to perform the cover removing using the base cutout than grasping the wings.

Applicant's Root Cause Analysis

There are two root causes for the close call: cover design and small font/image size. First, the design of the cutout visually cues a user that has not read the PI, to place a finger or thumb there to assist with cover removal. Doing so allows a user to slightly flex the cover to easily release it from the vial adapter. Moreover, the slightly angled surface of the wings might not be noticed and/or understood by the user and the angled surface of the wings can be difficult for some to successfully grasp and squeeze. Second, Figure 5 in the PI presents the word "Wings" in a small font that is difficult to see. Moreover, the image does not clearly indicate the wings location and where a user should place her finger and thumb to squeeze in order to remove the cover.

Participants (b) (6) – Difficulty removing cover when not squeezing wings
(Operational Difficulty)

Summary

These participants had difficulty removing the cover because they either had difficulty identifying and finding the wings, or they grasped the cover on the opposite side as the wings. (b) (6) referred to the PI during first use. During the post task interview, (b) (6) said she read about the wings, but couldn't tell where to grab from the image provided in the PI. She thought that Figure 4 actually went with the content for Step 5, so she tried removing the adapter cover with the hand orientation used to affix the adapter to the vial. She also noted that "I would never read the whole sentence for a figure," which explains why she didn't notice the "(see Figure 5)" at the end of Step 5. Once the moderator explained that Figure 5 corresponded to Step 5, (b) (6) was able to successfully complete the task. (b) (6), who did not consult the PI while completing the task, stated that "I didn't squeeze the wings; I just lifted straight up." When asked why, she noted, "I guess it's because of the way I was holding it when I put it on." When redirected to use the PI, the participant was able to successfully complete the task. (b) (6) squeezed the opposite sides of the VA cover at first. She stated that she was not sure where the wings were, but after feeling around a bit, she corrected her hand position, squeezed the wings and released the packaging. She said "it was hard to tell on the picture exactly where to squeeze the wings because the fingers are covering the vial adapter. An additional image that shows the wings more clearly would be good. In Figure 5, show the VA cover by itself with arrows pointing to the wings (no fingers on it)." (b) (6) removed the VA cover by squeezing the side of the rim of the VA cover, rather than the wings. She noted that Figures 4 and 5 on the PI are unclear because they seem to show the hand turning the VA cover while it is on the vial to remove it. This is because the hand position in Figure 4 is different from the hand position in Figure 5, but it was not evident to this user that the two figures are meant

to show a change in hand position (i.e., one position to put VA on and a different hand orientation to remove the cover, with fingers now on the wings). (b) (6) struggled a bit to remove the vial adapter cover, but was eventually successful. She looked at the PI for 60 seconds only prior to using the system. Because she looked at the PI so briefly, she was not aware of the need to squeeze the wings, but after handling the vial adapter cover a bit, she found the wings and successfully removed the cover.

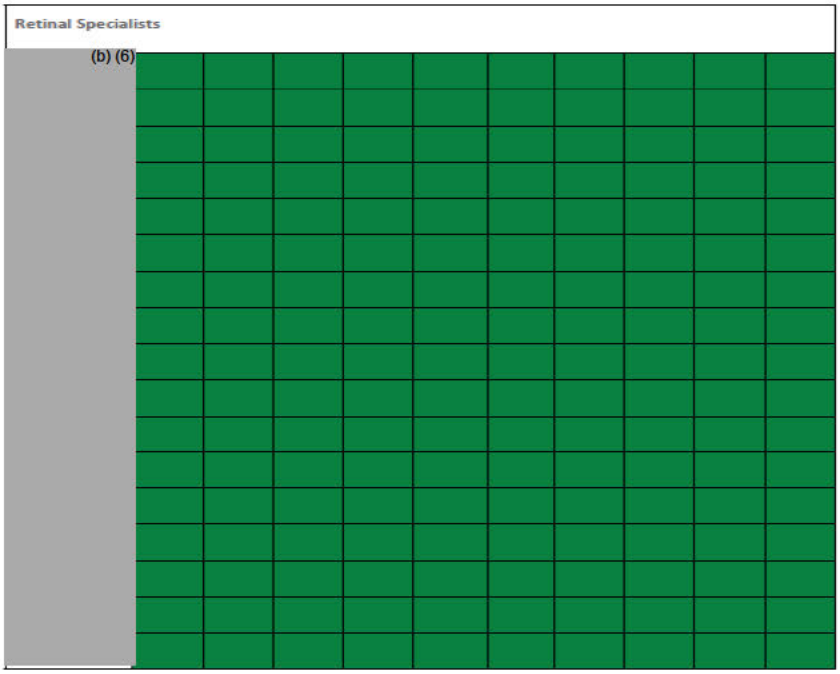
Applicant's Root Cause Analysis

There are two potential root causes for the close call: vial adapter cover design and PI design. The cover design makes it easier to grasp the non-wings vs. the wings side. Moreover, it is not intuitive that a user would need to change finger/thumb placement to remove the cover. This is only reliably discovered by reading the PI. The PI design, with small font and images closely located between two steps can make it confusing to quickly determine the corresponding image and step.

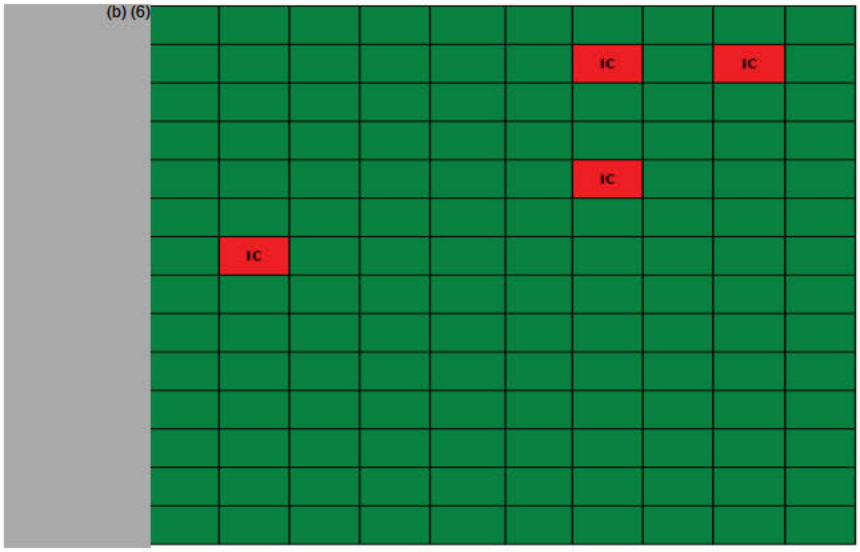
Labeling Comprehension Questions

Table 8. Labeling Comprehension Questions

	Correct	IC	Incorrect



Participant	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Health Care Professionals (includes Ophthalmic Technicians and Nurses)										
(b) (6)										



Summary

The findings from this study demonstrate that the intended users of this product can safely and successfully prepare doses using the current labeling. Participants demonstrated that they understood about the safe and effective storage, handling, and preparation of EYLEA:

- All knew what contents were contained in the carton.
- All but one knew to store the carton in the refrigerator.
- All were able to find and report the correct expiration date and lot number.
- All were able to explain how to remove the protective seal from the vial adapter cover.
- All knew that the vial adapter should not be removed from the vial adapter cover with their fingers.
- All knew that it was not necessary to remove the vial adapter from the cover prior to affixing to the vial.
- All but two knew that you have to attach the vial adapter to the vial to remove it from the cover.
- All knew that an audible click indicated that the vial adapter is firmly attached to the vial.
- All knew that an audible click indicated that the vial adapter is firmly attached to the vial.
- All but one knew that you needed to squeeze the wing to release the vial from the cover.

NOTE: In the cases of the two participants who removed the vial adapter from the cover with their fingertips while wearing gloves – it was clear that prior training and their routine work-contexts impacted their behaviors. Specifically, they both noted that it is their typical workflow to remove sterile items from packaging prior to surgery, thus it made sense to follow the same procedure when presented with a vial adapter in a sterile packaging.

- In addition, both of these participants typically work in OR contexts. And they both removed the vial adapter with their fingers without looking at the PI.
- When asked to complete the task again using the PI, both were able to perform the task successfully.

NOTE: In the cases of the two participants who detached the vial adapter after inserting into the vial while attempting to remove the cover – two causes appear to be relevant:

- First, the design of the vial adapter cover did not clearly communicate to these users how to squeeze the wings for proper removal; and second,
- The small size of the illustrations provided in the PI (especially Figures 4 and 5) made it challenging to visualize the removal process.
- However, both participants were able to determine this was an error, self-corrected, and then correctly used the wings to release the cover from the vial adapter once it was again affixed to the vial.

- Moreover, both users noted that they would be able to easily use it correctly on their second attempt.

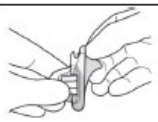
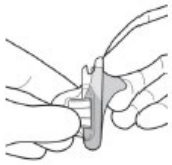
Reviewer's Comments:

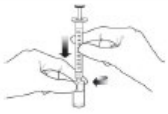
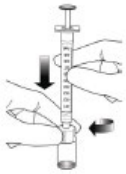
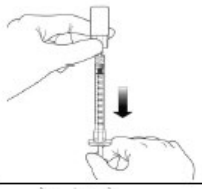
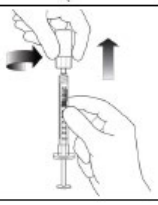
The study notes multiple occasions when the participants were confused by the provided labeling, but the applicant initially claimed that the PI was not revised based on participant feedback regarding these errors. The Conclusion in Section 8.0 of the report states that the findings from this study demonstrate that the intended users of this product can safely and successfully prepare doses using the current (i.e. proposed) labeling. An Information Request was sent to the applicant ton 8/4/2106:

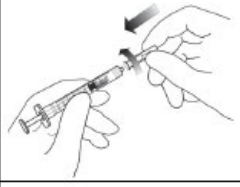
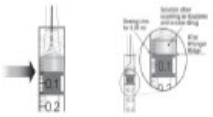
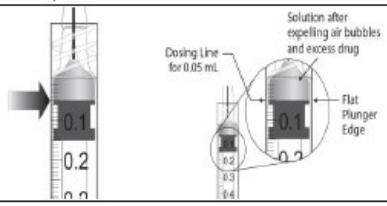
FDA IR # 1. Please provide an explanation why the observed errors (noted below) related to the text and figures provided in the package insert did not warrant revision to the proposed PI.

Regeneron Response:
The findings from the labeling comprehension study demonstrate that the intended users of this product can safely and successfully prepare doses using the provided instructions for use and do not warrant revision of the proposed language in the prescribing information (PI). However, following the labeling comprehension study, minor formatting revisions were made to the illustrations and captions in the Preparation for Administration section of the PI (Section 2.6). In addition, the size of all illustrations in the printed PI will be increased by approximately 60%. Because these revisions did not change the content of the labeling, further testing of the PI is not considered necessary. Table 1 compares the version of the PI tested in the labeling comprehension study and the PI that was included in the PAS submission.

Table 1: Revisions to Prescribing Information Preparation for Administration (Instructions for Use)

Step	Illustration Used in Labeling Comprehension Study	Illustration in Proposed PI (see Module 1.14.1.3)	Minor Formatting Revisions Include
01			1. Updated line weight (i.e., the thickness of the lines in the illustration) of vial and hands to match 2. Updated scale and proportion of vial and vial solution to match 3. Added gradient to top of vial cover for accuracy (the top of the vial cover is not white) 4. Revised the shading of the vial solution to appear darker. **All changes are formatting changes only; no changes to content have been made**
02			1. Updated line weight of (i.e, the thickness of the lines in the illustration) vial and hands to match 2. Updated scale and proportion of vial and vial solution to match 3. Revised the shading of the vial solution to appear darker **All changes are formatting changes only; no changes to content have been made**
03			1. Updated line weight (i.e., the thickness of the lines in the illustration) of vial adapter and hands to match **All changes are formatting changes only; no changes to content have been made**

Step	Illustration Used in Labeling Comprehension Study	Illustration in Proposed PI (see Module 1.14.1.3)	Minor Formatting Revisions Include
06			1. Updated line weight (i.e., the thickness of the lines in the illustration) of vial and hands to match 2. Updated scale and proportion of vial and vial solution to match 3. Revised the shading of the vial solution to appear darker **All changes are formatting changes only; no changes to content have been made**
07			1. Updated piston appearance to other steps 2. Updated scale and proportion of vial and vial solution to match **All changes are formatting changes only; no changes to content have been made**
08			1. Updated piston appearance to other steps 2. Updated scale and proportion of vial and vial solution to match **All changes are formatting changes only; no changes to content have been made**

Step	Illustration Used in Labeling Comprehension Study	Illustration in Proposed PI (see Module 1.14.1.3)	Minor Formatting Revisions Include
09			1. Updated piston appearance to other steps 2. Updated scale and proportion of vial solution to match **All changes are formatting changes only; no changes to content have been made**
10			1. Updated piston appearance to other steps 2. Updated scale and proportion of vial solution to match **All changes are formatting changes only; no content changes have been made**
11a & 11b			1. Updated piston appearance to other steps 2. De-coupled the image and the text; typesetter matches font size of the text to the caption to increase prominence of the text 3. Increased the size of the text **All changes are formatting changes only; no content changes have been made**

Step	Illustration Used in Labeling Comprehension Study	Illustration in Proposed PI (see Module 1.14.1.3)	Minor Formatting Revisions Include
04			1. Updated line weight (i.e., the thickness of the lines in the illustration) of vial and hands to match 2. Updated scale and proportion of vial and vial solution to match 3. Revised the shading of the vial solution to appear darker **All changes are formatting changes only; no changes to content have been made**
05			1. Updated line weight (i.e., the thickness of the lines in the illustration) of vial and hands to match 2. Updated scale and proportion of vial and vial solution to match 3. De-coupled the image and the text; typesetter matches font size of the text to the caption to increase prominence of the text 4. The "wings" callout text is relocated in two areas, to appear next to the arrows indicating where the vial adapter packaging should be squeezed. Dotted lines pointing to the wings were removed. 5. Revised the shading of the vial solution to appear darker **All changes are formatting changes only.**

FDA IR i. Regarding Participants (b) (6) – Uncertainty regarding where the vial adapter fit in the delivery system (Operational Difficulty): On page 27 of the report you state, (b) (6) *was confused by the PI images and where to place the vial adapter. The image in Figure 4 appeared to show the vial adapter attached to the end of the syringe."*

Regeneron Response 1.i:
Although these participants experienced operational difficulty while removing the protective seal and pushing the vial adapter spike into the rubber stopper on top of the vial until it locks in place, they were all ultimately able to perform the task successfully. Their successful completion of the tasks does not warrant further revision to the proposed PI.

- (b) (6): This participant did not read the PI therefore her performance was not a reflection on the effectiveness of the PI. The participant was able to quickly overcome the operational difficulty without moderator intervention and successfully performed the task after the initial difficulty.
- (b) (6): The operational difficulty experienced by this participant appears to be a test artifact; rather than being uncertain about the use of the vial adapter, the participant did not want to remove the cap from the vial because it would waste "…a really expensive medication." Once the participant was told that he should open the vial and referred to the PI, he successfully completed the task.
- (b) (6): This participant did experience difficulty; however his difficulty did not result in a use error. He was ultimately able to perform the task without moderator intervention.

FDA IR ii. Regarding Participants (b) (6) – Vial adapter initially dislodged from vial when removing cover (Use Error). On page 28 of the report you state, ***"The root cause of this error for both participants appears to be that the images in Figures 4 and 5 did not effectively communicate the location of the "wings" described in the text of the instructions. (b) (6) stated that he was mostly using the text on the PI to guide him, rather than the images in the associated figures, but he further noted that Figures 4 and 5 were not clear and he did not understand to what the term wings referred. The participant (31 years old) did not see the words "wings" that are written below the Vial Adapter in Figure 5 until the moderator provided him with a magnifying glass. (b) (6) also indicated that the images would have communicated more effectively if they were bigger, or if there was an additional call-out image (in Figure 3, 4, or 5) of the Vial Adapter with arrows clearly indicating the wings. This participant also observed that in Figures 4 and 5 it is difficult to see how the fingers are positioned relative to the geometry of the VA cover because it is difficult to see the wings versus the fingers. "I did not see those as wings. I saw that in the text, but didn't know what it referred to." After the moderator provided a magnifying glass, she further noted "Oh now I see the arrows pointing to the wings, but I did not see them before. Even with the magnifying glass I can barely see the dotted lines. If the image were bigger it would communicate better, or add an image next to it with arrows pointing to the wings." For users who are unfamiliar with vial adapters, as these participants were, the process of squeezing the "wings" is not initially intuitive and the current PI images are not sufficiently helpful in communicating this process."***

Regeneron Response 1.ii:
Both participants experienced use errors while squeezing the wings on the vial adapter cover to remove it. The participants immediately recognized the error and were able to

correct it independently. The overall occurrence of these use errors was low (2 of the 33 participants, a 6% use error rate). Notably, all participants, including participants (b) (6) and (b) (6), were ultimately able to withdraw all of the vial contents into the syringe. When presented with a second opportunity to use the vial adapter, participants (b) (6) performed the tasks without difficulty. After the participants completed the study, the moderator inquired about the use errors to determine the root cause. The participants then noted their difficulties with the figures in the PI and the moderator provided a magnifying glass to participant (b) (6). As described above, following the study, changes were made to figure 5 of the PI to more effectively communicate the location of the wings, addressing the root cause of the errors observed. Further, the size of all figures (including Figure 4 and Figure 5) in the printed PI will be increased by approximately 60%.

Figure 5, as tested (actual size)

New Figure 5

FDA IR iii. Regarding Participant (b) (6) – Vial adapter partially dislodged from vial when removing cover (Close Call). On page 28/29 of the report you state, "*There are two root causes for the close call: cover design and small font/image size. First, the design of the cutout visually cues a user that has not read the PI, to place a finger or thumb there to assist with cover removal. Doing so allows a user to slightly flex the cover to easily release it from the vial adapter. Moreover, the slightly angled surface of the wings might not be noticed and/or understood by the user and the angled surface of the wings can be difficult for some to successfully grasp and squeeze. Second, Figure 5 in the PI presents the word "Wings" in a small font that is difficult to see. Moreover, the image does not clearly indicate the wings location and where a user should place her finger and thumb to squeeze in order to remove the cover.*"

Regeneron Response 1.iii:
This participant, ophthalmic technician (b) (6), experienced a "close call" while squeezing the wings on the vial adapter cover to remove it; however, she was able to complete the task. The "close call" occurred while removing the cover from the affixed vial adapter. The participant admitted that she did not read the PI for Step 5, which is the step with which she experienced difficulties. When asked to complete the task again, the participant was able to successfully remove the cover from the affixed vial adapter, invert the vial and draw all vial contents into the syringe. In addition, as described above, changes were made to Figure 5 of the PI to decouple the word "wings" from the image and have the typesetter match the font to the caption, increasing the prominence of the text and more clearly identifying the location of the wings.

FDA IR iv. Regarding Participants (b) (6) – Difficulty removing cover when not squeezing wings (Operational Difficulty) On page 30 of the report you state, *"There are two potential root causes for the close call: vial adapter cover design and PI design. The cover design makes it easier to grasp the non-wings vs. the wings side. Moreover, it is not intuitive that a user would need to change finger/thumb placement to remove the cover. This is only reliably discovered by reading the PI. The PI design, with small font and images closely located between two steps can make it confusing to quickly determine the corresponding image and step."*

Regeneron Response 1.iv:
Although these participants experienced operational difficulty while removing the cover, they were all ultimately able to perform the task successfully. Their successful completion of the tasks does not warrant a revision to the proposed PI.

- (b) (6): This participant did experience difficulty; however her difficulty did not result in a use error. She was ultimately able to perform the task successfully.
- (b) (6): This participant did not consult the PI therefore her performance is not a reflection of the PI effectiveness. She was able to perform the task successfully.
- (b) (6): This participant did experience difficulty; however her difficulty did not result in a use error. She was ultimately able to perform the task successfully without intervention.
- (b) (6): This participant did experience difficulty; however her difficulty did not result in a use error. She was ultimately able to perform the task successfully.
- (b) (6): This participant did not read the PI for a lengthy enough period, which resulted in her operational difficulty. She was able to perform the task successfully without intervention.

Sponsor Conclusion of the EYLEA Vial Adapter Kit Labeling Comprehension Study
Participants in this study demonstrated that the intended users of this product can safely and successfully prepare doses using the PI provided. The results of the study demonstrated that all participants, including those who experienced difficulty using the vial adapter, were able to withdraw the contents of the vial into the syringe so that a dose could be prepared.

Overall in the study there was only a 6% use error rate related to the second task of squeezing the wings on the vial adapter cover to remove. Given the very low error rate, the study's findings are considered to be acceptable. The findings from the labeling comprehension study demonstrate that the intended users of this product can safely and successfully prepare doses using the labeling provided.

Reviewer's Comments:

Contrary to the initial statements from the applicant, the labeling was revised. The applicant has provided their reasoning and their proposed revisions to the package insert. The revised package insert (Appendix) is acceptable.

Recommended Regulatory Action:

The revised package insert (see Appendix this review) and carton are acceptable. This supplement is recommended for approval provided there are no remaining CMC issues with this adaptor.

Sonal D. Wadhwa, MD
Medical Officer

APPENDIX

Following is the clean, revised package insert and carton/container submitted by the applicant on 6/30/2016.

Revisions have been made to the PI:

1. Recent Major Changes in Highlights
2. Sub Section 6.6
3. Sub Section 2.7
4. Section 16
5. Applicant Information at end of insert.

Revisions have been made to the carton:

1. Revised Carton Contents section

(b) (4)

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/s/

WILLIAM M BOYD
10/28/2016
Placed into DARRTS for Sonal Wadhwa, M.D.

Clinical Review of BLA 125387
Supplement 053- Review #2

BLA 125387/S-053
SDN-558

Submission Date: 10/25/16
Received Date: 10/25/16
Review Date: 10/26/16

Applicant: Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
914-345-7926

Applicant's Representative: Candace Drumma
Manager, CMC Regulatory Affairs

Drug: Eylea (aflibercept) Injection

Pharmacologic Category: anti-VEGF

Submitted:

Reference is made to Regeneron's Prior Approval Supplement submission dated June 30, 2016, for the replacement of the filter needle with the (b) (4) vial adapter. Regeneron is seeking approval from the Agency to replace the current filter needle with (b) (4) "vial adapter" inside the Eylea vial carton. The vial adapter will be used to transfer liquid drug product from the primary container (vial) into the delivery syringe. This operation is currently carried out with the filter needle.

Reference is also made to the CBE Labeling Supplement (S-052) updating the USPI to detail hypersensitivity reactions reported postapproval, for which approval was received October 24, 2016. As a consequence of the approval , Regeneron is amending the draft labeling for S-053.

DBRRI/OBP/CDER Review

The Division of Biotechnology Review and Research I (DBBRI) recommends approval of S-053 in their review dated 10/26/2016 in Panorama. There are no outstanding quality issues.

See Medical Officer's Review #1 of S-053 dated 10/28/16.

Following is the revised draft labeling for S-053 submitted by the applicant on 10/25/16 in SDN-558.

27 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

WILLIAM M BOYD
10/28/2016
Placed into DARRTS for Sonal Wadhwa, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s053

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Puglisi, Michael

From: Puglisi, Michael
Sent: Tuesday, October 18, 2016 9:54 AM
To: 'Candace Drumma'
Subject: Quality Reviewer's Information Request for BLA 125387/S-053

Hi Candace,

Below please find an information request from our Quality Reviewer for the June 30, 2016, supplement to the Eylea BLA which proposes replacement of the filter needle with [redacted] (b) (4) "vial adapter" inside the EYLEA vial carton. Please confirm receipt and provide an estimate on the timing of your response. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Information Request:
The cover letter indicates that the proposed [redacted] (b) (4) *vial adapter is intended to be packaged with EYLEA drug product vials manufactured at the* [redacted] (b) (4) *sites. However, not all relevant Module 3 sections for the* [redacted] (b) (4) *sites were updated with information related to the introduction of the vial adapter. The information provided in the BLA should be complete for each manufacturing site and should be consistent, with the exception of site-specific information. Update the relevant* [redacted] (b) (4) *sections (e.g., Sections 3.2.P.3.3 and/or 3.2.P.7) to include information regarding the secondary packaging, vial adapter and filter needle, as appropriate. Where applicable, the sections could be updated through the cross-referencing of relevant information included in Section 3.2.P VEGF Trap-Eye,* [redacted] (b) (4) *and 40 mg/mL Vials* [redacted] (b) (4) *).*

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/s/

MICHAEL J PUGLISI
10/18/2016

Puglisi, Michael

From: Puglisi, Michael
Sent: Thursday, August 04, 2016 9:36 AM
To: candace.drumma@regeneron.com
Subject: Clinical Reviewer's Information Request re: 6/30/16 Supplement to BLA 125387

Hi Candace,

Below please find an information request from our clinical reviewers re: the June 30, 2016, PAS to the Eylea BLA. This supplement provides for replacement of the filter needle with the (b) (4) vial adapter.
Please confirm receipt and let me know when you think you can provide this information. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

The Eylea package insert (PI) utilized in the Human Factors Validation Labeling Comprehension Study for the Eylea (aflibercept) Injection Vial and Vial Adapter appears to be identical to that proposed in this supplemental application.

The study notes multiple occasions when the participants were confused by the provided labeling, but the PI was not revised based on participant feedback regarding these errors. Your Conclusion in Section 8.0 of the report states that the findings from this study demonstrate that the intended users of this product can safely and successfully prepare doses using the current (i.e. proposed) labeling.

1. **Please provide an explanation why the observed errors (noted below) related to the text and figures provided in the package insert did not warrant revision to the proposed PI.**

   i. Regarding Participants (b) (6) – Uncertainty regarding where the vial adapter fit in the delivery system (Operational Difficulty):

   On page 27 of the report you state, "(b) (6) *was confused by the PI images and where to place the vial adapter. The image in Figure 4 appeared to show the vial adapter attached to the end of the syringe."*

   ii. Regarding Participants (b) (6) – Vial adapter initially dislodged from vial when removing cover (Use Error)

   On page 28 of the report you state, *"The root cause of this error for both participants appears to be that the images in Figures 4 and 5 did not effectively communicate the location of the "wings"*

described in the text of the instructions. [redacted] *stated that he was mostly using the text on the PI to guide him, rather than the images in the associated figures, but he further noted that Figures 4 and 5 were not clear and he did not understand to what the term wings referred. The participant (31 years old) did not see the words "wings" that are written below the Vial Adapter in Figure 5 until the moderator provided him with a magnifying glass.* [redacted] *also indicated that the images would have communicated more effectively if they were bigger, or if there was an additional call-out image (in Figure 3, 4, or 5) of the Vial Adapter with arrows clearly indicating the wings. This participant also observed that in Figures 4 and 5 it is difficult to see how the fingers are positioned relative to the geometry of the VA cover because it is difficult to see the wings versus the fingers. "I did not see those as wings. I saw that in the text, but didn't know what it referred to." After the moderator provided a magnifying glass, she further noted "Oh now I see the arrows pointing to the wings, but I did not see them before. Even with the magnifying glass I can barely see the dotted lines. If the image were bigger it would communicate better, or add an image next to it with arrows pointing to the wings." For users who are unfamiliar with vial adapters, as these participants were, the process of squeezing the "wings" is not initially intuitive and the current PI images are not sufficiently helpful in communicating this process."*

iii. Regarding Participant [redacted] – Vial adapter partially dislodged from vial when removing cover (Close Call)

On page 28/29 of the report you state, *"There are two root causes for the close call: cover design and small font/image size. First, the design of the cutout visually cues a user that has not read the PI, to place a finger or thumb there to assist with cover removal. Doing so allows a user to slightly flex the cover to easily release it from the vial adapter. Moreover, the slightly angled surface of the wings might not be noticed and/or understood by the user and the angled surface of the wings can be difficult for some to successfully grasp and squeeze. Second, Figure 5 in the PI presents the word "Wings" in a small font that is difficult to see. Moreover, the image does not clearly indicate the wings location and where a user should place her finger and thumb to squeeze in order to remove the cover."*

iv. Regarding Participants [redacted] – Difficulty removing cover when not squeezing wings (Operational Difficulty)

On page 30 of the report you state, *"There are two potential root causes for the close call: vial adapter cover design and PI design. The cover design makes it easier to grasp the non-wings vs. the wings side. Moreover, it is not intuitive that a user would need to change finger/thumb placement to remove the cover. This is only reliably discovered by reading the PI. The PI design, with small font and images closely located between two steps can make it confusing to quickly determine the corresponding image and step."*

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/s/

MICHAEL J PUGLISI
08/04/2016