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

1 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)

2 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 5 injections 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)

6 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)

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)

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See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2016

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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 (14.2), (14.3)]. 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 (14.1)]. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

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 12 weeks (3 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 12 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

The glass vial is for single use only.

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

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

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

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

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

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

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

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

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

10. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).
Each vial should only be used for the treatment of a single eye. If the Counseling Information (17). Intravitreal injection, including with EYLEA [5.2 Increase in Intraocular Pressure Information (17)].

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

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

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

### Figure 6:

![Diagram of a vial and syringe for EYLEA](image)

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

### Figure 7a:

![Diagram showing the injection procedure](image)

### Figure 7b:

![Diagram showing the dosing line for 0.05 mL](image)

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, filter, 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)].
Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>CRVO (N=218)</th>
<th>Control (N=142)</th>
<th>EYLEA (N=91)</th>
<th>Control (N=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye pain</td>
<td>13%</td>
<td>5%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>12%</td>
<td>11%</td>
<td>20%</td>
<td>4%</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>8%</td>
<td>6%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Corneal epithelium defect</td>
<td>5%</td>
<td>4%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>5%</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Ocular hyperemia</td>
<td>5%</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>3%</td>
<td>5%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>3%</td>
<td>4%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Laceration</td>
<td>3%</td>
<td>4%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>3%</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>1%</td>
<td>&lt;1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Intraocular inflammation</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Cataract</td>
<td>&lt;1%</td>
<td>1%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>&lt;1%</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Baseline to Week 52</th>
<th>Baseline to Week 100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EYLEA (N=578)</td>
<td>Control (N=287)</td>
</tr>
<tr>
<td>eye pain</td>
<td>28%</td>
<td>17%</td>
</tr>
<tr>
<td>conjunctival hemorrhage</td>
<td>9%</td>
<td>6%</td>
</tr>
</tbody>
</table>
cataract                           | 8%                  | 9%                   |
vitreous floaters                   | 6%                  | 3%                   |
corneal epithelium defect           | 5%                  | 3%                   |
intraocular pressure increased      | 5%                  | 3%                   |
ocular hyperemia                    | 5%                  | 6%                   |
vitreous detachment                 | 3%                  | 3%                   |
foreign body sensation in eyes      | 3%                  | 3%                   |
laceration increased                | 3%                  | 2%                   |
vision blurred                      | 2%                  | <1%                  |
intraocular inflammation           | 2%                  | 2%                   |
injection site pain                 | 2%                  | <1%                  |
eyelid edema                       | <1%                 | 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.

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, gastrochisis, cleft palate, 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.

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 (PIGF) 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. PIGF 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.

Afibercept acts as a soluble decoy receptor that binds VEGF-A and PIGF, 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, GALLLEO, 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 afibercept: VEGF complex. Once absorbed into the systemic circulation, afibercept presents in the plasma as free afibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., afibercept: VEGF complex).

Absorption/Distribution
Following intravitreal administration of 2 mg per eye of EYLEA to patients with wet AMD, RVO, and DME, the mean Cmax of free afibercept 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 afibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Afibercept 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 afibercept is more than 100 fold lower than the concentration of afibercept required to half-maximally bind systemic VEGF.

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

Metabolism/Elimination
Afibercept is a therapeutic protein and no drug metabolism studies have been conducted. Afibercept 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 afibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg afibercept.

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 afibercept 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 afibercept. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of afibercept 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 lutal 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 afibercept 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 afibercept 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, multicenter, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluated 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

<table>
<thead>
<tr>
<th>VIEW1</th>
<th>VIEW2</th>
</tr>
</thead>
<tbody>
<tr>
<td>EYLEA 2 mg Q8 weeks</td>
<td>EYLEA 2 mg Q4 weeks</td>
</tr>
<tr>
<td>Full Analysis Set</td>
<td>N=301</td>
</tr>
</tbody>
</table>

Efficacy Outcomes

Proportion of patients who maintained visual acuity (%) (<15 letters of BCVA loss)

| Differencea (%) (95.1% CI) | 0.6 (3.3, 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

| Differenceb (%) (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 (%)

| Differencec (%) (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 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

Table 5: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in COPERNICUS and GALILEO Studies

<table>
<thead>
<tr>
<th>COPERNICUS</th>
<th>GALILEO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>EYLEA 2 mg Q4 weeks</td>
</tr>
<tr>
<td>N=73</td>
<td>N=114</td>
</tr>
</tbody>
</table>

Efficacy Outcomes

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.

14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The safety and efficacy of EYLEA were assessed in two randomized, multicenter, double-masked, sham-controlled studies in patients with macular edema following CRVO. A total of 358 patients were treated and evaluated 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.

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 1:1:1 ratio to either 2 mg EYLEA administered every 4 weeks (Q4) 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

<table>
<thead>
<tr>
<th>Efficacy Outcomes</th>
<th>VIBRANT</th>
<th>EYLEA 2 mg Q4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)</td>
<td>26.7%</td>
<td>52.7%</td>
</tr>
<tr>
<td>Weighted Difference (95% CI)</td>
<td>26.6% (13.0, 40.1)</td>
<td></td>
</tr>
<tr>
<td>Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)</td>
<td>6.9 (12.9)</td>
<td>17.0 (11.9)</td>
</tr>
<tr>
<td>Difference in LS mean (95% CI)</td>
<td>10.5 (7.1, 14.0)</td>
<td></td>
</tr>
</tbody>
</table>

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

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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>EYLEA 2 mg Q8 weeks</th>
<th>EYLEA 2 mg Q4 weeks</th>
<th>Control</th>
<th>EYLEA 2 mg Q8 weeks</th>
<th>EYLEA 2 mg Q4 weeks</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIVID</td>
<td>N=135</td>
<td>N=136</td>
<td>N=132</td>
<td>N=151</td>
<td>N=154</td>
<td>N=154</td>
</tr>
<tr>
<td>Efficacy Outcomes at Week 52</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>9.1 (6.3, 11.8)</td>
<td>9.3 (6.5, 12.0)</td>
<td>10.5 (7.7, 13.2)</td>
<td>12.2 (9.4, 15.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)</td>
<td>33.3%</td>
<td>32.4%</td>
<td>9.1%</td>
<td>31.1%</td>
<td>41.6%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Adjusted Difference (95% CI)</td>
<td>24.2% (13.5, 34.9)</td>
<td>23.3% (12.6, 33.9)</td>
<td>23.3% (13.5, 33.1)</td>
<td>34.2% (24.1, 44.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Efficacy Outcomes at Week 100

<table>
<thead>
<tr>
<th>Study</th>
<th>EYLEA 2 mg Q8 weeks</th>
<th>EYLEA 2 mg Q4 weeks</th>
<th>Control</th>
<th>EYLEA 2 mg Q8 weeks</th>
<th>EYLEA 2 mg Q4 weeks</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIVID</td>
<td>N=135</td>
<td>N=136</td>
<td>N=132</td>
<td>N=151</td>
<td>N=154</td>
<td>N=154</td>
</tr>
<tr>
<td>Efficacy Outcomes at Week 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>8.2 (5.2, 11.3)</td>
<td>10.7 (7.6, 13.8)</td>
<td>10.1 (7.0, 13.3)</td>
<td>10.6 (7.1, 14.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)</td>
<td>31.1%</td>
<td>38.2%</td>
<td>12.1%</td>
<td>33.1%</td>
<td>38.3%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Adjusted Difference (95% CI)</td>
<td>19.0% (8.0, 29.9)</td>
<td>26.1% (14.8, 37.5)</td>
<td>20.1% (9.6, 30.6)</td>
<td>25.8% (15.1, 36.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 10: Mean Change in Visual Acuity from Baseline to Week 24 in VIBRANT Study

Mean Change in Visual Acuity (ETDRS Letter Score)

Weeks

4 8 12 16 20 24

EYLEA 2 mg Q4 weeks

Control Group

Mean Change in Visual Acuity (ETDRS Letter Score)

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.
VISTA studies are shown in Table 8 below.

Results from the analysis of ETDRS-DRSS at week 100 in the VIVID and compared to the control group. Significantly greater in both EYLEA treatment groups (2Q4 and 2Q8) when proportion of patients improving by at least 2 steps on the ETDRS-DRSS was diabetic retinopathy (NPDR) based on the ETDRS-DRSS. At week 100, the enrolled in these studies (77%) had moderate-to-severe nonproliferative diabetic retinopathy (DR) and DME at baseline. The majority of patients see Clinical Studies (14.4)

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>
<thead>
<tr>
<th>Evaluable Patients</th>
<th>EYLEA 2 mg Q8 weeks</th>
<th>EYLEA 2 mg Q4 weeks</th>
<th>Control</th>
<th>EYLEA 2 mg Q8 weeks</th>
<th>EYLEA 2 mg Q4 weeks</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=101</td>
<td>N=97</td>
<td>N=99</td>
<td>N=148</td>
<td>N=153</td>
<td>N=150</td>
<td></td>
</tr>
<tr>
<td>Number of patients with a ≥2-step improvement on ETDRS-DRSS from baseline (%)</td>
<td>32 (32%)</td>
<td>27 (28%)</td>
<td>7 (7%)</td>
<td>56 (38%)</td>
<td>58 (38%)</td>
<td>24 (16%)</td>
</tr>
<tr>
<td>Difference (%) (97.5% CI)</td>
<td>24% (12, 36)</td>
<td>21% (9, 33)</td>
<td>22% (11, 33)</td>
<td>22% (11, 33)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The number of evaluable patients included all patients who had valid ETDRS-DRSS data at baseline

Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors

Difference is EYLEA minus Control group

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)].

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

Storage

EYLEA should be refrigerated at 2°C to 8°C (36°F to 46°F). 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
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