EYLEA® (aflibercept) Injection, for Intravitreal Injection
Initial U.S. Approval: 2011

INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR) in Patients with DME

DOSAGE AND ADMINISTRATION

The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, 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 (approximately every 25 days, 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). (2.2, 2.4, 2.5)

EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, 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). (2.2, 2.4, 2.5)

The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 25 days, monthly). (2.3)

Risk of Arterial Thromboembolic Events
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

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

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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.

A 5-micron sterile filter needle (19-gauge × 1½-inch), a 1-mL Luer lock syringe and a 30-gauge × ½-inch sterile injection needle are needed.

EYLEA is available packaged as follows:
• Vial Kit with Injection Components (filter needle, syringe, injection needle) [see How Supplied (16)].

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 (approximately every 28 days, 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 (approximately every 25 days, 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). Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.

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 (approximately every 25 days, 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 (approximately every 28 days, 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 (approximately every 25 days, 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 (approximately every 28 days, 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 (approximately every 25 days, 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.

The glass vial is for single use only.

EYLEA is available packaged as follows:
• Vial Kit with Injection Components (filter needle, syringe, injection needle) [see How Supplied (16)].

Use aseptic technique to carry out the following preparation steps:
1. Remove the protective plastic cap from the vial (see Figure 1).

Figure 1:

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

Figure 2:

3. Remove the 19-gauge × 1½-inch, 5-micron, filter needle and the 1-mL syringe from their packaging. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see Figure 3).

Figure 3:

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

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

Figure 4a:

Figure 4b:

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

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

8. Remove the 30-gauge × ½-inch injection needle from its packaging and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 5).
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 compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. 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 detachment, vitreous floaters, and endophthalmitis or retinal detachment without delay and should be managed appropriately.

5.3.1 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, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1) [see Clinical Studies (14.1)]. Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.
Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Baseline to Week 52</th>
<th>Baseline to Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EYLEA (N=1824)</td>
<td>Active Control (ranibizumab) (N=1595)</td>
</tr>
<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>7%</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>
<tr>
<td>Retinal detachment</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

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

Macular Edema Following Retinal Vein Occlusion (RVO)

The data described below reflect 6 months exposure to EYLEA in 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 3: Most Common Adverse Reactions (≥1%) in DME Studies

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</tr>
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<td>8%</td>
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</tr>
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<td>Vitreous floaters</td>
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<td>3%</td>
</tr>
<tr>
<td>Corneal epithelium defect</td>
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</tr>
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<td>Eyelid edema</td>
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<td>1%</td>
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</table>

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

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [see Animal Data].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [see Clinical Pharmacology (12.1)], treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg. Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectodactyly, 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 not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential

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

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [see Nonclinical Toxicology (13.1)].

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
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 (aflibercept) Injection is a sterile, clear, and colorless to pale yellow solution. EYLEA is supplied as a preservative-free, sterile, aqueous solution for intravitreal injection in a single-dose, glass vial designed to deliver 0.05 mL (50 micrograms) of solution containing 2 mg 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 leukocytes. 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 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 during the first year.

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) for free aflibercept 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, multicenter, 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, up to week 52, 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). Protocol-specified visits occurred every 28±3 days. 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. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1. 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></th>
<th>VIEW1</th>
<th>VIEW2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<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>
<td>N=304</td>
</tr>
</tbody>
</table>

Efficacy Outcomes

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

<table>
<thead>
<tr>
<th></th>
<th>94%</th>
<th>95%</th>
<th>94%</th>
<th>95%</th>
<th>95%</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference^ (%)</td>
<td>(95.1% CI)</td>
<td>(-3.2, 4.4)</td>
<td>(2.4, 5.0)</td>
<td>(-2.9, 4.0)</td>
<td>(-4.0, 3.3)</td>
<td></td>
</tr>
<tr>
<td>Mean change in BCVA measured by ETDRS letter score from Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.9</td>
<td>10.9</td>
<td>8.1</td>
<td>8.9</td>
<td>7.6</td>
<td>9.4</td>
</tr>
<tr>
<td>Difference^ (%)</td>
<td>(95.1% CI)</td>
<td>(-2.0, 2.5)</td>
<td>(0.9, 5.4)</td>
<td>(-3.1, 1.3)</td>
<td>(-4.1, 0.2)</td>
<td></td>
</tr>
</tbody>
</table>

* Patient dosing schedules were individualized from weeks 52 to 96 using a modified 12-week dosing regimen.

VIEW1 and VIEW2 studies were both 96 weeks in duration. However after 52 weeks patients no longer followed a fixed dosing schedule. Between week 52 and week 96, patients continued to receive the drug and dosage strength to which they were initially randomized on a modified 12 week dosing schedule (doses at least every 12 weeks and additional doses as needed). Therefore, during the second year of these studies there was no active control comparison arm.

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 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. Protocol-specified visits occurred every 28±7 days. 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**

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

**Efficacy Outcomes**

- Proportion of patients who gained at least 15 letters in BCVA from Baseline (%): 12% (COPERNICUS Control) vs 56% (COPERNICUS EYLEA 2 mg Q4 weeks), 22% (GALILEO Control) vs 60% (GALILEO EYLEA 2 mg Q4 weeks).
- Weighted Difference (95.1% CI): 44.8% (32.9, 56.6) (COPERNICUS) vs 38.3% (24.4, 52.1) (GALILEO).
- Mean change in BCVA as measured by ETDRS letter score from Baseline (SD): -4.0 (18.0) (COPERNICUS) vs 17.3 (12.8) (GALILEO).
- Difference in LS mean (95.1% CI): 21.7% (17.3, 26.1) (COPERNICUS) vs 14.7% (10.7, 18.7) (GALILEO).

* Difference is EYLEA 2 mg Q4 weeks minus Control
* 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)
* p<0.01 compared with Control
* 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, and baseline retinal perfusion status) in the study 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). Protocol-specified visits occurred every 28±7 days. 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 control group could receive EYLEA.

In the VIBRANT study, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score. 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

<table>
<thead>
<tr>
<th></th>
<th>VIVID</th>
<th>VISTA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EYLEA 2 mg Q8 weeks</td>
<td>EYLEA 2 mg Q4 weeks</td>
</tr>
<tr>
<td>Full Analysis Set</td>
<td>N=135</td>
<td>N=136</td>
</tr>
</tbody>
</table>

Efficacy Outcomes at Week 52

Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)

<table>
<thead>
<tr>
<th></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>Differenceb,c in LS mean</td>
<td>9.1± (9.7, 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>(97.5% CI)</td>
<td>(6.3, 11.8)</td>
<td>(6.5, 12.0)</td>
<td>(7.7, 13.2)</td>
<td></td>
<td>(9.4, 15.0)</td>
<td></td>
</tr>
</tbody>
</table>

Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)

<table>
<thead>
<tr>
<th></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>Adjusted Differenced,e</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>
<tr>
<td>(97.5% CI)</td>
<td>(12.6, 33.9)</td>
<td>(13.5, 33.1)</td>
<td>(24.1, 44.4)</td>
<td></td>
<td>(34.2, 44.4)</td>
<td></td>
</tr>
</tbody>
</table>

Efficacy Outcomes at Week 100

Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)

<table>
<thead>
<tr>
<th></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>Differencef,g in LS mean</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>(97.5% CI)</td>
<td>(2.6, 11.0)</td>
<td>(10.0, 14.3)</td>
<td>(9.0, 13.4)</td>
<td></td>
<td>(10.6, 15.6)</td>
<td></td>
</tr>
</tbody>
</table>

Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)

<table>
<thead>
<tr>
<th></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>Adjusted Differenceh,i</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>
<tr>
<td>(97.5% CI)</td>
<td>(11.4, 33.7)</td>
<td>(14.8, 37.5)</td>
<td>(9.6, 30.6)</td>
<td></td>
<td>(15.1, 36.6)</td>
<td></td>
</tr>
</tbody>
</table>

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 Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors.
e After treatment initiation with 5 monthly injections
f 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.
g Difference is EYLEA group minus Control group
h Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors.
i After treatment initiation with 5 monthly injections
j The number of evaluable patients included all patients who had valid ETDRS-DRSS data at baseline
k Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors.
l After treatment initiation with 5 monthly injections
m Difference is EYLEA group minus Control group
n After treatment initiation with 5 monthly injections

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) in VIVID and VISTA Studies

<table>
<thead>
<tr>
<th></th>
<th>VIVID</th>
<th>VISTA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EYLEA 2 mg Q8 weeks</td>
<td>EYLEA 2 mg Q4 weeks</td>
</tr>
<tr>
<td>Evaluable Patients</td>
<td>N=101</td>
<td>N=97</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>
</tr>
<tr>
<td>Differencej,k (%)</td>
<td>24% (13.6, 36.6)</td>
<td>21% (9.3, 33.9)</td>
</tr>
<tr>
<td>(97.5% CI)</td>
<td>(12.6, 33.9)</td>
<td>(9.3, 33.9)</td>
</tr>
</tbody>
</table>

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 After treatment initiation with 5 monthly injections
g Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors
h After treatment initiation with 5 monthly injections
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 Kit with Injection Components</td>
<td>one EYLEA 2 mg/0.05 mL single-dose glass vial one 19-gauge × 1½-inch, 5-micron, filter needle for withdrawal of the vial contents one 30-gauge × ½-inch injection needle for intravitreal injection one 1-mL syringe for administration one package insert</td>
</tr>
</tbody>
</table>

Storage
Refrigerate EYLEA at 2ºC to 8ºC (36ºF to 46ºF). Do Not Freeze. Do not use beyond the date stamped on the carton and container label. Store in the original carton until time of use to protect from light.

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.