EYLEA® (aflibercept) Injection is indicated for the treatment of patients with neovascular (Wet) Age-related Macular Degeneration (AMD). It is also indicated for the treatment of patients with Macular Edema following Central Retinal Vein Occlusion (CRVO).

EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or any of the excipients in EYLEA.

Please see Important Prescribing and Safety Information on back cover and the accompanying full Prescribing Information.
Today, the second most common cause of retinal vascular disease is retinal vein occlusion. Although central retinal vein occlusion (CRVO) accounts for a minority of retinal vein occlusions, CRVO is associated with more severe vision loss and a higher risk of neovascular glaucoma. The characteristic clinical picture of CRVO (Fig. 1) – scattered hemorrhages throughout the retina, cotton-wool spots, massive edema, venous dilatation and tortuosity, and fluorescein angiographic findings of reduced blood flow, retinal wall staining, and leakage of dye into the retina – reflects the presence of an obstruction in the central retinal vein, partially blocking blood outflow from the retina. The likely source of the blockage is a thrombus, the formation of which is triggered by atherosclerotic vessel wall damage or, in some cases, inflammation that creates a thrombogenic environment in the adjacent vein.

Compromised outflow from the central retinal vein increases intraluminal pressure in the venous bed distal to the thrombus, causing extravasation of fluid and blood into surrounding tissues. The lack of lymphatic vessels to drain excess fluid from the retina makes the retina highly vulnerable to the consequences of macular edema. Marked retinal edema increases interstitial pressure that may interfere with capillary flow and retinal perfusion. When the pressure of edematous interstitial fluid exceeds intraluminal pressure, capillaries may collapse and close, as in capillaries with relatively low intraluminal pressure fed by atherosclerotic arterioles. Although little or no capillary closure is classified as perfused CRVO while extensive capillary nonperfusion is classified as nonperfused CRVO, nonperfusion and ischemia actually represent a continuum from mild to severe.

The natural history of untreated CRVO is characterized by generally poor (<20/40) visual acuity that decreases over time. Vision morbidity in CRVO is primarily due to macular edema, posterior neovascularization leading to vitreous hemorrhage, anterior segment neovascularization, and neovascular glaucoma as potential complications. The risk of neovascular complications increases in the presence of severe ischemia; nonischemic eyes can evolve to ischemic eyes in up to one-third of affected eyes.

Although the standard of care in macular edema following CRVO has been careful observation, several intravitreal agents have been approved for use in patients with macular edema following CRVO based on randomized, masked, sham-controlled trials.

Recognized for their angiogenic effects, members of the VEGF family of proteins – namely VEGF-A, which activates VEGF receptors 1 (VEGFR-1) and 2 (VEGFR-2), and placental growth factor (PlGF), which activates VEGFR-1 – are also vascular permeability factors that can play a role in edema formation. Indeed, VEGF proved to be the same molecule as “vascular permeability factor” (VPF), which was shown in preclinical studies to be more than 50,000 times as potent as histamine in causing microvascular permeability.

Upregulation of VEGF-A and PlGF, as well as VEGFR-1 and VEGFR-2 expression, by hypoxic conditions that can arise with compromised retinal perfusion suggest a potential role of these cytokines in macular edema following CRVO. Many of the pathologic anatomic changes associated with ischemic retinal disorders such as CRVO were replicated when VEGF was injected intravitreally into the eyes of adult primates, including venous dilation and tortuosity, vascular leakage, edema, and microaneurysms. VEGF also triggered regional ischemia via capillary closure, suggesting that VEGF levels could be increased by a positive feedback loop initiated with upregulation of VEGF expression. Clinically, a number of studies have measured aqueous humor VEGF-A concentrations in patients with various intraocular vascular diseases, including neovascular (wet) age-related macular degeneration (AMD) and macular edema in ischemic and nonischemic CRVO. Aqueous VEGF-A concentrations in patients with CRVO were at least an order of magnitude higher than in controls (patients with no detectable ocular vascular disease undergoing, for example, macular hole surgery) and also much higher than in patients with wet AMD (Fig. 2). According to several studies, aqueous VEGF-A concentrations in CRVO correlated with the severity of macular edema.

The observations of

Figure 1. Clinical presentation of CRVO as seen with funduscopy (A), fluorescein angiography (B), and optical coherence tomography, OCT (C). Fundus examination typically reveals characteristic “blood and thunder” retina, i.e., hemorrhages, cotton-wool spots, and edema in all quadrants in combination with dilated, tortuous veins. Fluorescein angiography is characterized by delayed filling of retinal veins, leakage of dye into the retina, and capillary perfusion defects while OCT allows an assessment of macular edema severity. Images courtesy of Jason Slakter, MD.

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VEGFR-2 – domains critical for ligand contact and binding.40-42 The two-arm trap configuration of aflibercept is supported by the constant Fc (Fragment, crystallizable) region of IgG1.39 Aflibercept acts as a soluble decoy receptor, trapping VEGF-A and PlGF to prevent interactions with native cell-surface receptors.43

The complex formed when aflibercept traps VEGF is inactive and stable. Studies of the relative serum concentrations of free aflibercept and aflibercept:VEGF complex following systemic administration in animal models have provided insight into the dynamics of endogenous VEGF intraocular blockade. These studies demonstrated that after drug administration, the aflibercept:VEGF complex accumulated rapidly as aflibercept trapped target ligands and free aflibercept was converted to bound complex. The level of aflibercept:VEGF complex plateaued at maximal concentrations when sufficient aflibercept was present to bind the total pool of endogeneous VEGF being produced by the tissues. With further increases in dose, free aflibercept concentrations increased in a dose-dependent manner since no more VEGF was available for binding with aflibercept. These observations suggested that the local VEGF pool would be completely neutralized as long as free aflibercept levels exceeded aflibercept:VEGF complex levels.45

Disposition of aflibercept following intravitreal aflibercept injection in patients is expected to follow a course in which a fraction of the administered dose sequesters endogenous VEGF-A or PlGF to form the inactive aflibercept-ligand complex (target-mediated elimination), with both free (active) and inactive aflibercept being absorbed into the systemic circulation for elimination via proteolysis.45 The predominant form of aflibercept in circulation is the inactive complex. Maximal plasma concentrations of free aflibercept (mean, 0.05 µg/mL; range, 0 to 0.081 µg/mL) occurred 1 to 3 days after a 2 mg intravitreal aflibercept injection in patients with CRVO and were below detectable limits within 2 weeks post-dosing in

higher aqueous VEGF-A concentrations in macular edema with CRVO relative to wet AMD, for example, are consistent with the amount of retinal tissue potentially compromised by an obstruction in the central retinal vein.

However, the most compelling clinical evidence of the pathologic role of VEGF-A came from a randomized, sham-controlled trial in which an anti-VEGF therapy significantly improved visual acuity in patients with macular edema following CRVO.14,15 A significant negative correlation between baseline aqueous VEGF-A concentrations and visual acuity improvements was observed in an open-label study of an anti-VEGF therapy. Most patients in this study had no residual macular edema after intravitreal anti-VEGF injections. Aqueous levels of other cytokines tested did not differ in patients with residual edema vs. those without edema after anti-VEGF therapy, suggesting that these specific cytokines were not major contributors to macular edema in these patients. Thus, VEGF appears to be a major contributor to macular edema following CRVO.

**Trap Technology and Aflibercept**

Cytokine traps38,39 such as aflibercept are molecules based on propriety technology developed at Regeneron Pharmaceuticals. In the case of aflibercept, the trap-like arms (Fig. 3) are each composed of the second extracellular ligand-binding domain from human VEGFR-1 fused to the third extracellular ligand-binding domain from human VEGFR-2 – domains critical for ligand contact and binding.40-42 The two-arm trap configuration of aflibercept is supported by the constant Fc (Fragment, crystallizable) region of IgG1.39 Aflibercept acts as a soluble decoy receptor, trapping VEGF-A and PlGF to prevent interactions with native cell-surface receptors.43

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**Important Safety Information for EYLEA® (aflibercept) Injection**

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. 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. Intraocular inflammation has been reported with the use of EYLEA.
almost all patients. With intravitreal aflibercept injections at 4-week intervals, free aflibercept did not accumulate in plasma. After 2 mg intravitreal aflibercept, it is estimated that mean maximal plasma concentrations of free aflibercept were more than 100-fold lower than the concentration required to half-maximally bind systemic VEGF-A.

**COPERNICUS**\(^{16,17}\) and **GALILEO**\(^{18,19}\) Studies

The efficacy and safety of intravitreal aflibercept injection (IAI), known commercially as EYLEA® (aflibercept) Injection, in the treatment of macular edema following CRVO was evaluated in two randomized, double-masked, sham-controlled Phase 3 trials of similar design: the COPERNICUS (Controlled Phase 3 Evaluation of Repeated Intravitreal Administration of VEGF Trap-Eye In Central Retinal Vein Occlusion: Utility and Safety) study\(^{16,17}\) and the GALILEO (General Assessment Limiting Infiltration of Exudates in Central Retinal Vein Occlusion with VEGF Trap-Eye) study.\(^{18,19}\) In the absence of an approved treatment for macular edema following CRVO when the studies were designed, the studies were sham-controlled for the primary analysis at 24 weeks.\(^{16,18}\)

Centers from six countries, including the United States and Canada, participated in COPERNICUS; GALILEO was conducted at centers in Europe and the Asian/Pacific region. Nearly 400 treatment-naïve patients were enrolled in the two studies. Key criteria for patient participation were center-involved macular edema, CRVO diagnosis within 9 months of study entry, Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) ≥20/40 and <20/320 Snellen equivalent and mean central retinal thickness ≥250 µm on optical coherence tomography (OCT) at baseline. Patients with signs suggestive of advanced retinal ischemia were not excluded, allowing enrollment of patients with nonperfused CRVO.\(^{16,18}\)

Patients were randomized 3:2 to intravitreal aflibercept injection 2 mg monthly (every 4 weeks, 2Q4) or sham control injections monthly for 24 weeks, the cut-off point for the primary analysis. After the first 24 weeks, masked treatment continued with all patients initially randomized to monthly 2 mg intravitreal aflibercept in the COPERNICUS and GALILEO studies transitioned to as-needed (pro re nata, PRN) injections according to protocol-defined retreatment criteria. However, the studies differed in terms of those initially assigned to sham control injections, with those in the GALILEO study continuing monthly sham injections through 52 weeks and those in the COPERNICUS study crossing over to intravitreal aflibercept administration for the remainder of the study. If macular edema following CRVO progressed to neovascularization at any time during the study, patients could receive panretinal photocoagulation at the investigator’s discretion. Only the results of the primary analysis period with fixed 2Q4 dosing (initial 24 weeks) are discussed here.\(^{16,18,46}\)

The primary endpoint was the proportion of patients with ≥15-letter gain from baseline BCVA at 24 weeks. Secondary endpoints included BCVA change from baseline over 24 weeks and changes in central retinal thickness. Additional analyses examined treatment responses according to time since CRVO diagnosis (post-hoc analysis) and baseline perfusion status.\(^{16,18,46}\)

Demographic and baseline disease characteristics (Table 1) in patients participating in the COPERNICUS and GALILEO studies were similar within sham control and

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**Important Safety Information for EYLEA® (aflibercept) Injection**

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

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intravitreal aflibercept groups and consistent with expectations for patients with relatively newly diagnosed CRVO. At study entry, patients tended to have severe macular edema (i.e., mean central retinal thickness >650 µm) and poor visual acuity. The COPERNICUS study enrolled a larger proportion of patients with CRVO classified as nonperfused or indeterminate.\textsuperscript{16,18}

### Efficacy Outcomes

#### Primary Endpoint

For the primary endpoint (Fig. 4), 56% of patients receiving intravitreal aflibercept injection 2Q4 in the COPERNICUS study and 60% of those in the GALILEO study had gained $\geq 15$ ETDRS letters from baseline at 24 weeks, with both studies showing significant differences ($P<0.01$) between intravitreal aflibercept injection and sham control. Both the COPERNICUS and GALILEO studies demonstrated significant ($P<0.01$) differences favoring intravitreal aflibercept injection over sham control in proportion of patients with clinically significant improvements in visual acuity. The time course of response showed that a substantial proportion of patients responding to intravitreal aflibercept injection 2Q4 did so within the first 4 weeks, with response rates gradually increasing as injections continued, before plateauing at 16-20 weeks.\textsuperscript{16,18}

#### Visual Acuity Change from Baseline

As with the primary endpoint, mean change in visual acuity at week 24 also showed a robust treatment effect from intravitreal aflibercept injection 2Q4 (Fig. 5), with a 21.7 (COPERNICUS) and 14.7 (GALILEO) mean ETDRS letter difference favoring intravitreal aflibercept over sham injection ($P<0.01$ vs. sham control in both studies). The analysis of mean change from baseline BCVA mirrored the primary endpoint in that much of the visual acuity gain associated with intravitreal aflibercept injections occurred within 4 weeks of the first injection, plateauing at 16-20 weeks. In the COPERNICUS study, mean change from baseline BCVA declined over time in the sham control arm whereas, in the GALILEO study, it showed no or small increases from baseline BCVA. The majority of patients treated with intravitreal aflibercept injection 2Q4 in both studies (COPERNICUS, 94%; GALILEO, 89%) showed some ($\geq 20$ letters) improvement from baseline BCVA compared with substantially smaller proportions of patients in the sham control arms (COPERNICUS, 52%; GALILEO, 60%).\textsuperscript{16,18}

#### Impact of Disease Factors on Response

The impact of disease factors on efficacy measured as proportion of patients gaining $\geq 15$ ETDRS letters over 24 weeks was also evaluated. In a post-hoc analysis of

### Table 1. COPERNICUS and GALILEO Studies: Baseline Disease Characteristics\textsuperscript{16,18}

<table>
<thead>
<tr>
<th></th>
<th>Sham Control</th>
<th>Intravitreal Aflibercept Injection 2Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COPERNICUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (full analysis set)</td>
<td>73</td>
<td>114</td>
</tr>
<tr>
<td>CRVO diagnosis time, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq 2$ months</td>
<td>71%</td>
<td>56%</td>
</tr>
<tr>
<td>$&gt;2$ months</td>
<td>29%</td>
<td>43%</td>
</tr>
<tr>
<td>ETDRS BCVA letter score, mean (SD)</td>
<td>49 (14)</td>
<td>51 (14)</td>
</tr>
<tr>
<td>BCVA Snellen equivalent $\leq 20/200$, %</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>Central retinal thickness, mean (SD)</td>
<td>672 (245) µm</td>
<td>662 (237) µm</td>
</tr>
<tr>
<td>Perfusion status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfused*</td>
<td>68.5%</td>
<td>67.5%</td>
</tr>
<tr>
<td>Nonperfused</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>15%</td>
<td>17.5%</td>
</tr>
<tr>
<td><strong>GALILEO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (full analysis set)</td>
<td>68</td>
<td>103</td>
</tr>
<tr>
<td>CRVO diagnosis time, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;2$ months</td>
<td>51.5%</td>
<td>53%</td>
</tr>
<tr>
<td>$\geq 2$ months</td>
<td>48.5%</td>
<td>45%</td>
</tr>
<tr>
<td>ETDRS BCVA letter score, mean (SD)</td>
<td>51 (15)</td>
<td>54 (16)</td>
</tr>
<tr>
<td>BCVA Snellen equivalent $\leq 20/200$, %</td>
<td>18%</td>
<td>16.5%</td>
</tr>
<tr>
<td>Central retinal thickness, mean (SD)</td>
<td>639 (225) µm</td>
<td>683 (234.5) µm</td>
</tr>
<tr>
<td>Perfusion status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfused*</td>
<td>79%</td>
<td>86%</td>
</tr>
<tr>
<td>Nonperfused</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>10%</td>
<td>7%</td>
</tr>
</tbody>
</table>

*<10 disc areas of nonperfusion
Figure 4. Percent patients gaining ≥15 ETDRS letters from baseline at 24 weeks (primary endpoint) and time course of response.\textsuperscript{16,18} Weighted difference (intravitreal aflibercept injection 2Q4 minus sham control) for primary endpoint: COPERNICUS, 44.8%; GALILEO, 38.3% (P<0.01 vs sham control for both studies). Last observation carried forward; full analysis set.

COPERNICUS

Primary Endpoint

\[
\begin{array}{c|c|c}
\% \text{ of Patients} & \text{Sham Control} & \text{IAI 2Q4} \\
\hline
12\% & 73 & 114 \\
\hline
\end{array}
\]

Response Over Time

\[
\begin{array}{c|c|c}
\% \text{ of Patients} & 0 & 4 & 8 & 12 & 16 & 20 & 24 \\
\hline
\text{Sham Control} & 12\% & \uparrow & \uparrow & \uparrow & \uparrow & \downarrow & \downarrow \\
\text{IAI 2Q4} & 56\% & \uparrow & \uparrow & \uparrow & \uparrow & \downarrow & \downarrow \\
\hline
\end{array}
\]

GALILEO

Primary Endpoint

\[
\begin{array}{c|c|c}
\% \text{ of Patients} & \text{Sham Control} & \text{IAI 2Q4} \\
\hline
22\% & 68 & 103 \\
\hline
\end{array}
\]

Response Over Time

\[
\begin{array}{c|c|c}
\% \text{ of Patients} & 0 & 4 & 8 & 12 & 16 & 20 & 24 \\
\hline
\text{Sham Control} & 22\% & \uparrow & \uparrow & \uparrow & \uparrow & \downarrow & \downarrow \\
\text{IAI 2Q4} & 60\% & \uparrow & \uparrow & \uparrow & \uparrow & \downarrow & \downarrow \\
\hline
\end{array}
\]

Figure 5. Mean change from baseline in ETDRS BCVA from baseline over 24 weeks.\textsuperscript{16,18} Weighted difference (intravitreal aflibercept injection 2Q4 minus sham control) for mean BCVA improvement from baseline at 24 weeks: COPERNICUS, +21.3 ETDRS letters; GALILEO, +14.7 ETDRS letters (P<0.01 vs sham control for both studies). Last observation carried forward; full analysis set.

COPERNICUS

\[
\begin{align*}
\text{BCVA change from baseline, mean ETDRS letters} & : +17.3^{*} \\
\text{IAI 2Q4 (n=114)} & \\
\text{Sham Control (n=73)} & \text{+21.3 absolute difference} \quad \text{+4.0} \\
\hline
\end{align*}
\]

\[
\begin{align*}
\text{BCVA change from baseline, mean ETDRS letters} & : +18.0^{*} \\
\text{IAI 2Q4 (n=103)} & \\
\text{Sham Control (n=68)} & \text{+14.7 absolute difference} \quad \text{+3.3} \\
\hline
\end{align*}
\]

GALILEO

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response according to time since CRVO diagnosis (Fig. 6A), intravitreal aflibercept injection 2Q4 was effective across subsets in both the COPERNICUS and GALILEO studies. However, more patients experienced clinically significant gains in visual acuity when treatment was initiated within a 2-month window of CRVO diagnosis, suggesting a potential benefit of earlier intervention. When patients were grouped according to baseline perfusion status (perfusion defined as <10 disc areas of nonperfusion), a pre-specified analysis demonstrated that treatment response to intravitreal aflibercept injection 2Q4 was consistent across subsets, regardless of perfusion status (Fig. 6B). Likewise, mean ETDRS BCVA changes from baseline over 24 weeks associated with intravitreal aflibercept injection 2Q4 was consistent regardless of perfusion status.16,18,46

Figure 6. Percent patients gaining ≥15 ETDRS letters from baseline at 24 weeks according to time since CRVO diagnosis (post-hoc analysis) (A) and baseline perfusion status (B).16,18,46 Cut-off for time since CRVO diagnosis differed between studies (COPERNICUS, ≤2 vs >2 months; GALILEO, <2 vs ≥2 months). Perfusion defined as <10 disc areas of nonperfusion. In the analysis according to baseline perfusion status, patients with CRVO classified as indeterminate were included in the nonperfused subset. (The relatively small number of patients (n=14) may account for the seemingly higher response rate with intravitreal aflibercept injection in patients with nonperfused CRVO in the GALILEO study.) Last observation carried forward; full analysis set.

Important Safety Information for EYLEA® (aflibercept) Injection

There is a potential risk of arterial thromboembolic events (ATEs) following use of intravitreal VEGF inhibitors, including EYLEA, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of ATEs in the VIEW 1 and VIEW 2 wet AMD studies in patients treated with EYLEA was 1.8% during the first year. The incidence of ATEs in the COPERNICUS and GALILEO CRVO studies was 0% in patients treated with EYLEA compared with 1.4% in patients receiving sham control during the first six months.
Pharmacodynamic Effects of Intravitreal Aflibercept: Anatomic Changes

Anatomic measures were not used to influence treatment decisions in the COPERNICUS or GALILEO studies during the fixed-dose, 24-week period of monthly (4-week) double-masked drug administration (primary analysis). Changes in central retinal thickness as measured by OCT are regarded as pharmacodynamic effects of VEGF inhibition in macular edema following CRVO. After 24 weeks, reductions from baseline mean central retinal thickness were greater in patients receiving intravitreal aflibercept than in patients receiving sham control injections in both the COPERNICUS and GALILEO studies. The difference favoring intravitreal aflibercept injection emerged within 4 weeks after the first injection and was maintained with continued dosing (Fig. 7).

Tolerability and Safety of Intravitreal Aflibercept in Macular Edema Following CRVO

Across the COPERNICUS and GALILEO studies, 218 patients with macular edema following CRVO were treated with intravitreal aflibercept; 141 patients received sham injections. Of the six scheduled monthly injections, the mean number of injections was 5.7 in the intravitreal aflibercept group and 5.3 in the sham control group. The difference in mean number of injections reflected the larger proportion of patients in the intravitreal aflibercept arms completing 24 weeks of fixed-dose treatment (94% vs 80% in sham control arms).

The overall incidence of ocular adverse events was similar between groups (intravitreal aflibercept injection, 59%; sham control, 65%). Ocular adverse events were generally consistent with disease progression or the expected consequences of intravitreal injections. The most common adverse events occurring in ≥25% of patients receiving intravitreal aflibercept injection were eye pain, conjunctival hemorrhage, increased intraocular pressure, corneal erosion, vitreous floaters, and conjunctival hyperemia (Table 2). Increases in intraocular pressure (IOP) were adverse events reported by physicians and could include pre- and post-injection pressure increases. Use of IOP-lowering medication was not specified in these IOP increases since they were episodes reported as adverse events. Less common adverse events (<1%) were cataract, eyelid edema, corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Ocular adverse events leading to discontinuation were also more common in the sham control group than in those receiving intravitreal aflibercept injection (8% vs 1%), as were serious ocular adverse events (11% vs 3%). Serious ocular adverse events typically reflected worsening disease (e.g., vitreous hemorrhage, glaucoma, iris neovascularization) (Table 3). Serious nonocular adverse events occurred in 5.5% of patients treated with intravitreal aflibercept injection and 8% of those in the sham control group. No new safety signals associated with intravitreal aflibercept injection were observed in the macular edema following CRVO studies.

Figure 7. Anatomic changes measured as mean change from baseline central retinal thickness over 24 weeks. Last observation carried forward; full analysis set.
Because VEGF-A helps regulate vascular tone, increased blood pressure is believed to be one of the most sensitive biomarkers of endogenous VEGF-A inhibition systemically. In the COPERNICUS and GALILEO studies, blood pressures over the 24-week treatment period were similar in the intravitreal aflibercept and sham control groups, with mean systolic blood pressure decreasing slightly from baseline and mean diastolic blood pressure remaining stable. Although mean blood pressure did not increase, hypertension was reported as an adverse event. Using the

| Table 2. Most Common Adverse Events (≥1%) Over First 24 Weeks of CRVO Studies |
|---------------------------------|-----------------|

<table>
<thead>
<tr>
<th></th>
<th>Intravitreal Aflibercept Injection (N=218)</th>
<th>Sham Control (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye pain</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Corneal erosion</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Intraocular inflammation</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

| Table 3. Serious Ocular and Nonocular Adverse Events* Over First 24 Weeks of CRVO Studies |
|---------------------------------|-----------------|

<table>
<thead>
<tr>
<th></th>
<th>Intravitreal Aflibercept Injection (N=218)</th>
<th>Sham Control (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious ocular adverse event</td>
<td>3.2</td>
<td>11.3</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>0</td>
<td>3.5</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>0</td>
<td>2.8</td>
</tr>
<tr>
<td>Iris neovascularization</td>
<td>0.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>0.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>0</td>
<td>1.4</td>
</tr>
<tr>
<td>Macular edema</td>
<td>0</td>
<td>1.4</td>
</tr>
<tr>
<td>Any serious non-ocular adverse event</td>
<td>5.5</td>
<td>7.7</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>0.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Infections/infestations</td>
<td>0.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Injury/poisoning/procedural complications</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Respiratory/thoracic/mediastinal disorders</td>
<td>0.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Musculoskeletal/connective tissue disorders</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Renal/urinary disorders</td>
<td>0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Occurring in ≥2 patients

Important Safety Information for EYLEA® (aflibercept) Injection

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.
Antiplatelet Trialists’ Collaboration (APTC) criteria for classification of arterial thromboembolic events (ATEs) defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause), the incidence of ATEs during 24 weeks was 0% in patients receiving intravitreal aflibercept injection and 1.4% in the sham control group.

**Summary**

Development of macular edema is the most common cause of vision loss in CRVO. A number of studies measuring aqueous VEGF-A concentrations have demonstrated that VEGF-A production is markedly upregulated by decreased retinal perfusion such that VEGF-A levels are much higher in CRVO than in, for example, wet AMD or patients without detectable ocular vascular disease. The VEGF-A cytokines may actually be the primary stimulants of vascular leakage resulting in macular edema, based on preliminary observations.

Aflibercept is a fusion protein containing all human amino acid sequences that serves as a decoy receptor to trap the VEGFR-1 and VEGFR-2 ligands VEGF-A and PLGF and inhibit receptor signaling. Formulated as an iso-osmotic solution compatible with the intraocular environment, intravitreal aflibercept injection is a purified and formulated preparation of aflibercept, specifically for intravitreal injection. Intravitreal aflibercept injection is produced in recombinant Chinese hamster ovary (CHO) cells.

In the first 6 months of the COPERNICUS and GALILEO studies, intravitreal aflibercept injection was administered as 2 mg monthly (every 4 weeks). Based on the primary endpoint of proportion of patients with ≥15 ETDRS letter gain from baseline after 24 weeks, intravitreal aflibercept injection produced a robust treatment effect demonstrated by significantly more patients experiencing clinically relevant improvements in visual acuity relative to sham control injections. Much of the visual acuity gain occurred within 4 weeks of the first injection. The efficacy difference favoring intravitreal aflibercept injection over sham control was significant regardless of baseline perfusion status (perfused defined as <10 disc areas of nonperfusion). The COPERNICUS and GALILEO studies also showed that delayed treatment (>2 months) may adversely impact the treatment effect of anti-VEGF therapy.

The most common adverse events (≥25%) seen in the COPERNICUS and GALILEO studies in patients treated with intravitreal aflibercept injection were eye pain, conjunctival hemorrhage, increased intraocular pressure, corneal erosion, vitreous floaters, and conjunctival hyperemia. Serious ocular adverse events (e.g., vitreous hemorrhage, glaucoma, iris neovascularization) were consistent with worsening disease.

**References**


Please see Important Prescribing Information for EYLEA® (aflibercept) Injection on back cover and the accompanying full Prescribing Information


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**Important Safety Information for EYLEA® (aflibercept) Injection**

Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis, traumatic cataract, increased intraocular pressure, and vitreous detachment.
IMPORTANT PRESCRIBING INFORMATION FOR EYLEA® (aflibercept) INJECTION

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with neovascular (Wet) Age-related Macular Degeneration (AMD). The recommended dose for EYLEA is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

EYLEA is indicated for the treatment of patients with Macular Edema following Central Retinal Vein Occlusion (CRVO). The recommended dose for EYLEA is 2 mg administered by intravitreal injection every 4 weeks (monthly).

IMPORTANT SAFETY INFORMATION FOR EYLEA® (aflibercept) INJECTION

EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients of EYLEA.

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. 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. Intraocular inflammation has been reported with the use of EYLEA.

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

There is a potential risk of arterial thromboembolic events (ATEs) following use of intravitreal VEGF inhibitors, including EYLEA, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of ATEs in the VIEW 1 and VIEW 2 wet AMD studies in patients treated with EYLEA was 1.8% during the first year. The incidence of ATEs in the COPERNICUS and GALILEO CRVO studies was 0% in patients treated with EYLEA compared with 1.4% in patients receiving sham control during the first six months.

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

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

Please see accompanying full Prescribing Information.