EARLIER TREATMENT CAN MATTER FOR MACULAR EDEMA FOLLOWING RETINAL VEIN OCCLUSION

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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Disclosure: The author is a paid consultant to and has an ongoing relationship with Regeneron Pharmaceuticals, Inc. and/or its affiliates.

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INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

CONTRAINDICATIONS

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

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Introduction

After demonstrating strong efficacy in clinical trials, EYLEA® (aflibercept) Injection was approved by the US Food and Drug Administration (FDA) for the treatment of wet age-related macular degeneration (AMD) in 2011.[1] Since its approval, EYLEA has been evaluated in clinical trials and approved by the FDA for 3 other indications: diabetic macular edema (DME), macular edema following retinal vein occlusion (MEfRVO), and diabetic retinopathy (DR).[2] EYLEA is a treatment that targets vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). Research suggests that through its activation of VEGFR1, PlGF may play a potential role in promoting pathologic angiogenesis and vascular permeability, although a precise role continues to be investigated.[2-4]

Over the course of multiple clinical trials, EYLEA was studied in over 3000 patients for the treatment of certain retinal diseases.[5] More specifically, EYLEA has a demonstrated efficacy and safety profile in MEfRVO. Its molecular characteristics make EYLEA a strong treatment option for this disease.[2,6-8] In this supplement, we will cover these topics, along with the history of EYLEA and the significance of its development and demonstrated safety data to better understand EYLEA in the treatment of this high-VEGF burden retinal disease.

Development of EYLEA

Before anti-VEGF therapies were available, patients with MEfRVO had limited treatment options.[6] Following the positive efficacy and safety results from the Branch Retinal Vein Occlusion Study in 1984, laser photocoagulation was established as the standard of care for patients with macular edema following branch retinal vein occlusion (MEfBRVO)[9]; however, laser photocoagulation did not show the same efficacy results in patients with macular edema following central retinal vein occlusion (MEfCRVO) in the Central Vein Occlusion Study, which resulted in observation remaining the standard of care for these patients.[10] The next major development in therapies for MEfRVO was the use of intravitreal steroids. Both intravitreal triamcinolone acetonide and the dexamethasone intravitreal implant showed efficacy in patients with MEfRVO; however, they were associated with adverse events, including increases in intraocular pressure (IOP) and cataract formation.[11,12]

Research emerged in the late 20th century that characterized VEGF and demonstrated that its levels were increased in eyes with active neovascular disease.[13-15] Following these discoveries, the first clinical trials with anti-VEGF agents were initiated, which led to the approval of pegaptanib and ranibizumab for the treatment of wet AMD in 2004 and 2006, respectively.[16] A few years later, EYLEA was approved for the treatment of wet AMD.[1] Once approved to treat these patients, anti-VEGF agents were then investigated in MEfRVO.[6-8] EYLEA was approved by the FDA for the treatment of MEfCRVO in 2012 and MEfRVO in 2014.[17,18] The VIBRANT, COPERNICUS, and GALILEO clinical trials demonstrated that EYLEA was able to provide patients with a treatment option that showed significant improvement in visual and anatomic outcomes.[6-8]

SELECT IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

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.

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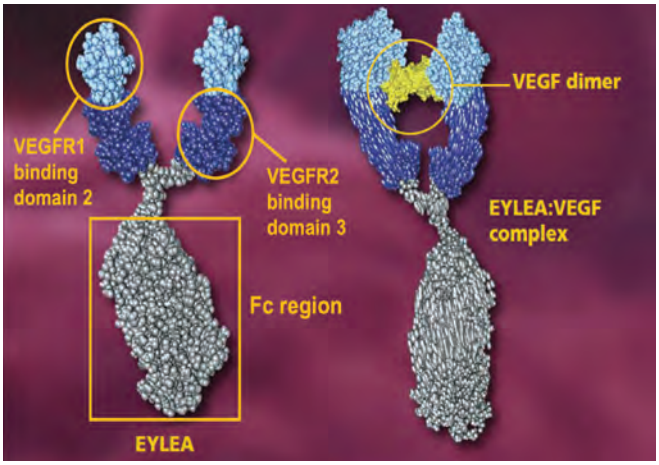

Figure 1: EYLEA Trap technology

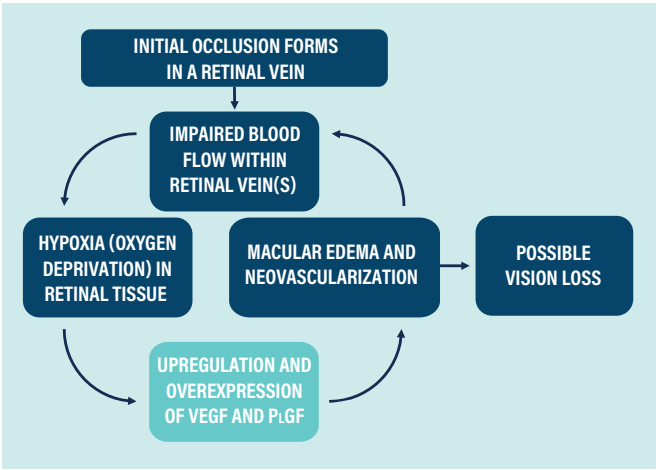

Figure 2: Hypothesized pathogenesis of MEfRVO

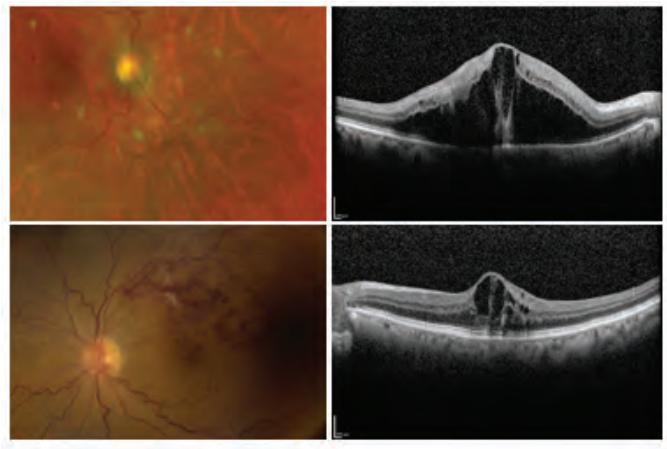

Figure 3: Fundus photographs (left) and OCT images (right) of eyes diagnosed with MEfCRVO (top) and MEfBRVO (bottom)

EYLEA is a fully human recombinant fusion protein of domains 2 and 3 of VEGFR1 and VEGFR2, respectively. These key domains are fused to the Fc portion of human immunoglobulin G, which acts as a decoy for the natural receptor that binds VEGF-A and PLGF dimers (Figure 1). EYLEA binds multiple isoforms of VEGF-A, VEGF-B, and PLGF to prevent their interaction with native VEGF receptors.[2,3] When activated by the binding of VEGF and PLGF, these receptors contribute to neovascularization and vascular permeability in retinal diseases.[19,20] Because of its trap design, EYLEA binds VEGF and PLGF in a 1:1 ratio, forming a stable inactive complex.[4]

Pathophysiology of MEfRVO

The hypothesized pathogenesis of MEfRVO (Figure 2) begins with an occlusion in a retinal vein, which impairs blood flow in the territory that is drained by that vein.[21] The impaired blood flow can cause hypoxia in the retinal tissues, triggering upregulation of VEGF and PLGF. PLGF is hypothesized to contribute to macular edema and neovascularization alongside VEGF.[21-23] Chronic macular edema and poor perfusion of perifoveal capillaries result in damage to macular photoreceptors, leading to vision loss.[21]

The overexpression of VEGF contributes to disease progression by worsening retinal ischemia, perpetuating the cycle of damage in MEfRVO.[24] Figure 3 illustrates how this pathophysiology can manifest in the eye of patients diagnosed with MEfCRVO and MEfBRVO through fundus photographs and optical coherence tomography (OCT) images.

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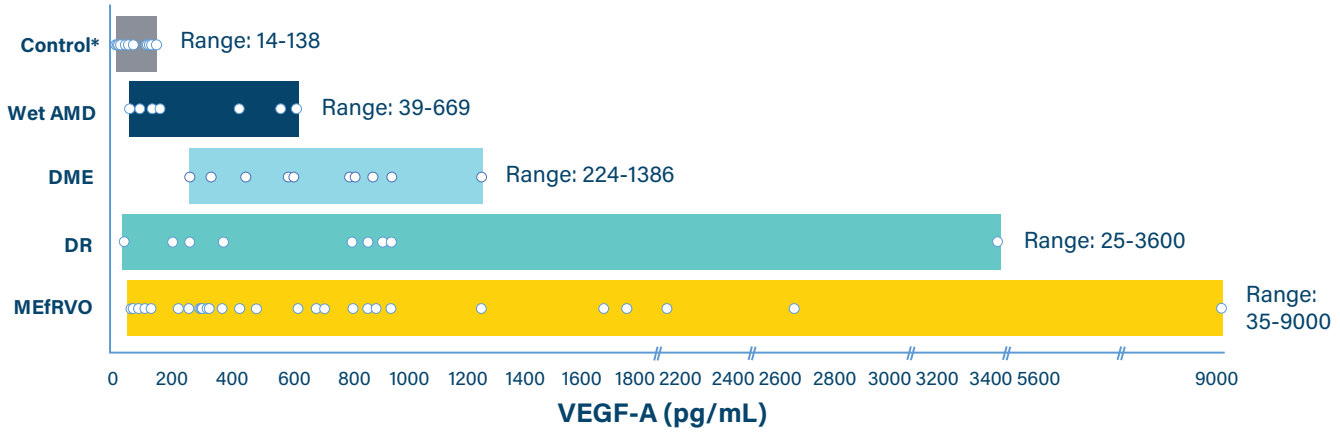

Figure 4: Upregulation of VEGF-A in wet AMD, DME, DR, and MEfRVO: range of reported mean values of vitreous and aqueous VEGF-A levels
*Controls in these studies included patients with cataract, macular hole, or epiretinal membrane in the absence of any retinal vascular disease.

Note that this graph shows the ranges of mean VEGF-A levels observed in studies of VEGF-related conditions.
All patients are different, and this graph may not be representative of any particular patient.

Additionally, studies have shown that VEGF-A is highly upregulated in retinal diseases, including wet AMD,[25-31] DME,[32-38] DR,[39-45] and, to a much greater extent, MEfRVO.[21,39,46-61] The expression of VEGF in patients with MEfRVO is up to 2.5 times greater than patients with DR, 6 times greater than patients with DME, and 13 times greater than patients with wet AMD (Figure 4).[21,25-61] PLGF is also upregulated 4.5- and 14.5-fold in MEfBRVO and MEfCRVO, respectively.[23,63]

EYLEA provides clinical efficacy

EYLEA was rigorously evaluated for efficacy and safety in the treatment of MEfBRVO (VIBRANT trial, N=181) and MEfCRVO (COPERNICUS trial, N=187; GALILEO trial, N=171).[2]

The VIBRANT trial was a randomized, multicenter, double-masked trial in patients with MEfBRVO.[2,6] Patients were randomly assigned in a 1:1 ratio to either EYLEA 2 mg every 4 weeks (Q4) or laser photocoagulation administered at baseline and subsequently as needed. The COPERNICUS and GALILEO trials were randomized, multicenter, double-masked trials in patients with MEfCRVO. Patients were randomly assigned in a 3:2 ratio to either EYLEA 2 mg Q4 or sham injections Q4.[2] Panretinal photocoagulation was available to all patients in both studies at any time during the study if they progressed to clinically significant ocular neovascularization.[6]

In the VIBRANT, COPERNICUS, and GALILEO trials, EYLEA met the primary endpoint of achieving a greater percentage of patients gaining ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at week 24 compared with control (53% vs 27% in VIBRANT, 56% vs 12% in COPERNICUS, and 60% vs 22% in GALILEO; $P<0.01$ for all) (Figure 5).[6-8]

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WARNINGS AND PRECAUTIONS

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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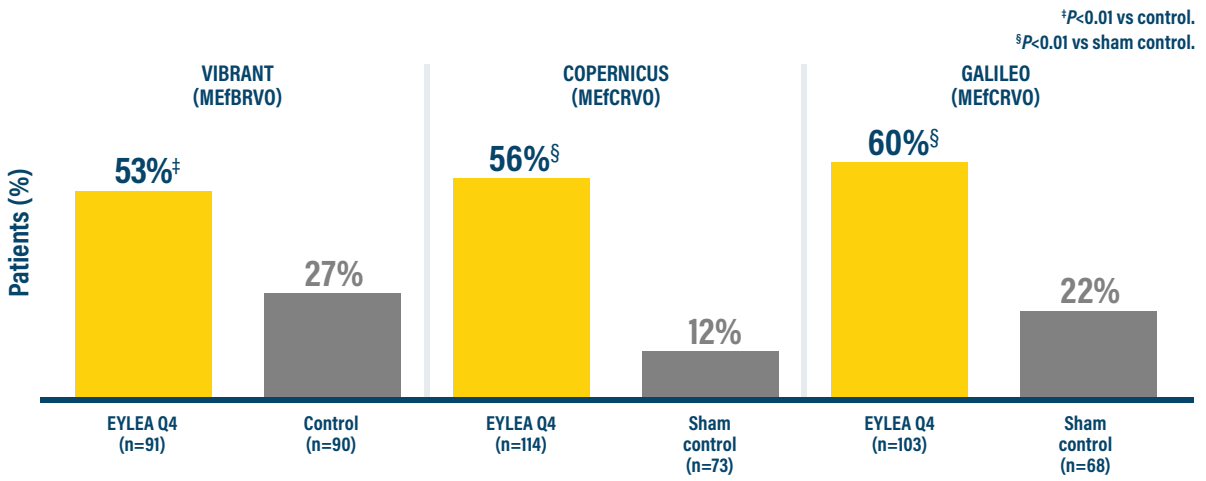

Figure 5: Percentage of patients who gained ≥15 ETDRS letters at 24 weeks (primary endpoint)†

†Last observation carried forward; full analysis set.

EYLEA also rapidly improved mean visual acuity (VA), which was maintained throughout the 24-week course of each study. The mean change in best-corrected visual acuity (BCVA), as measured by ETDRS letters, from baseline was significantly higher in the EYLEA groups vs the control groups at week 24 (17.0 vs 6.9 letters in VIBRANT, 17.3 vs -4.0 letters in COPERNICUS, and 18.0 vs 3.3 letters in GALILEO; *P*<0.01 for all) (Figure 6).[6-8]

Additionally, most patients in the trials experienced a VA improvement at 24 weeks. In the VIBRANT trial, the majority of patients (98%) in the EYLEA group maintained vision or gained >0 letters compared with 81% of patients in the control group.[6] In the COPERNICUS trial, the majority of patients (94%) in the EYLEA group maintained vision or gained >0 letters compared with 52% of patients in the sham control group.[7] In the GALILEO trial, the majority of patients (89%) in the EYLEA group maintained vision or gained >0 letters compared with 60% of patients in the sham control group.[8]

Whether patients presented with good or poor vision at baseline, EYLEA improved VA in patients with MEfRVO, as demonstrated by a prespecified subgroup analysis of the VIBRANT, COPERNICUS, and GALILEO studies (Figure 7).[7,64] Of patients in the EYLEA group with a VA >20/200 at baseline, 52% in VIBRANT, 52% in COPERNICUS, and 59% in GALILEO gained ≥15 letters. In the control groups, 27% of patients with a VA of >20/200 in VIBRANT, 11% in COPERNICUS, and 21% in GALILEO gained ≥15 letters. Of patients in the EYLEA group with a VA of ≤20/200 at baseline, 67% in VIBRANT, 68% in COPERNICUS, and 65% in GALILEO gained ≥15 letters. In the control groups, 29% of patients with a VA of ≤20/200 at baseline in VIBRANT, 17% in COPERNICUS, and 25% in GALILEO gained ≥15 letters.[7,64]

Because the prognosis of nonperfused MEfRVO tends to be poorer than perfused MEfRVO,[8] the VIBRANT, COPERNICUS, and GALILEO trials also analyzed the VA results in patients stratified by their baseline perfusion status.[7,64] Perfused was defined angiographically as <10 disc areas of retinal capillary nonperfusion, while nonperfused was defined as ≥10 disc areas of retinal capillary nonperfusion.[6-8] Among perfused patients in the EYLEA group, 44% in VIBRANT, 58% in COPERNICUS, and 58% in GALILEO gained ≥15 letters.

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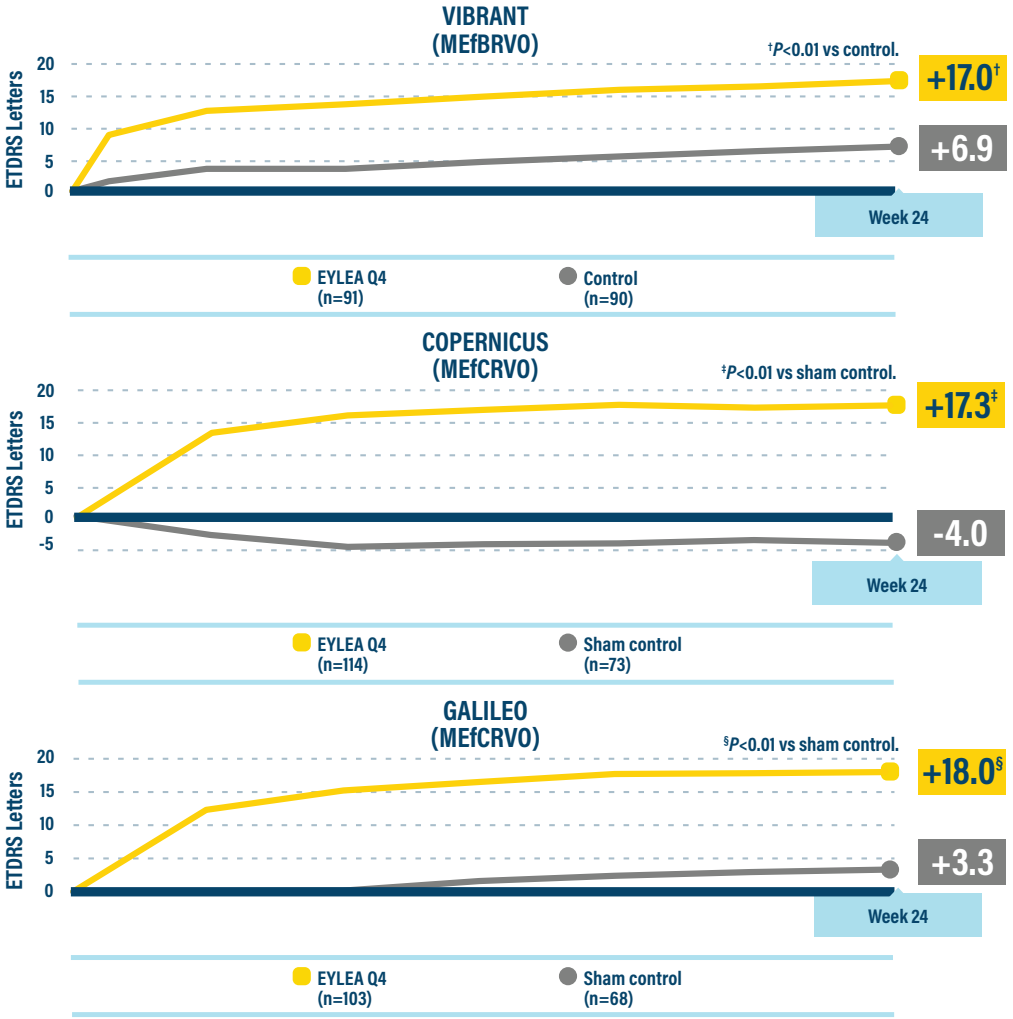

Figure 6: Mean change in BCVA through 24 weeks (secondary endpoint)*

*Last observation carried forward; full analysis set.

In the control groups, 24% of perfused patients in VIBRANT, 16% in COPERNICUS, and 26% in GALILEO gained ≥15 letters. Among nonperfused patients in the EYLEA groups, 60% in VIBRANT, 51% in COPERNICUS, and 71% in GALILEO gained ≥15 letters. In the control groups, 38% of nonperfused patients in VIBRANT, 4% in COPERNICUS, and 7% in GALILEO gained ≥15 letters. These analyses showed that EYLEA has a clinically significant effect in patients with MEfRVO regardless of baseline perfusion status.[7,64]

The improvement in VA seen with EYLEA was accompanied by a rapid and sustained decrease in central retinal thickness (CRT), as measured by OCT from baseline to week 24. The mean reduction in CRT from baseline was 280.5 µm in the EYLEA group vs 128.0 µm in the control group ($P<0.0001$) in VIBRANT, 457.2 µm in the EYLEA group vs 144.8 µm in the sham control group ($P<0.001$) in COPERNICUS, and 448.6 µm in the EYLEA group vs 169.3 µm in the control group ($P<0.0001$) in GALILEO at week 24 (Figure 8).[6-8]

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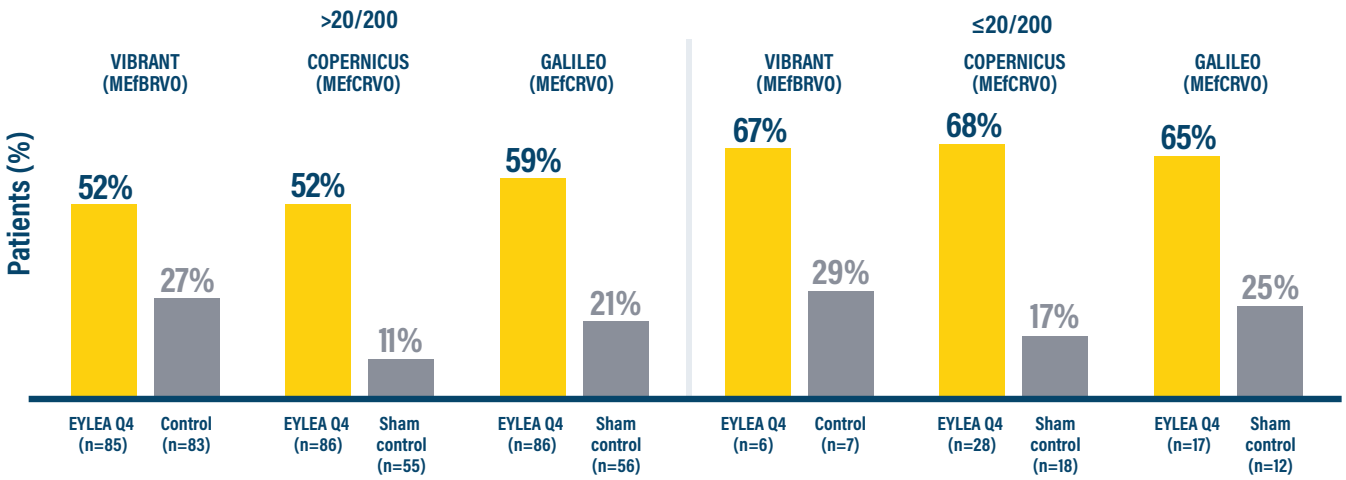

Figure 7: Percentage of patients who gained ≥15 ETDRS letters at 24 weeks by baseline VA (prespecified subgroup analysis)[II]

[II]Last observation carried forward; full analysis set.

Early treatment matters

The importance of early intervention in treating MEfRVO with EYLEA was demonstrated in the COPERNICUS and GALILEO trials. A protocol-specified subgroup analysis showed that patients assigned to the EYLEA group initiating treatment within 2 months of diagnosis demonstrated a 15-letter gain at 24 weeks compared with initiating treatment >2 months after diagnosis (69% vs 39% for COPERNICUS and 71% vs 50% for GALILEO) (Figure 9). In these clinical trials, improvements in VA were larger when the time to treatment was <2 months compared with ≥2 months.[7,8,64]

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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.

ADVERSE REACTIONS

Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.

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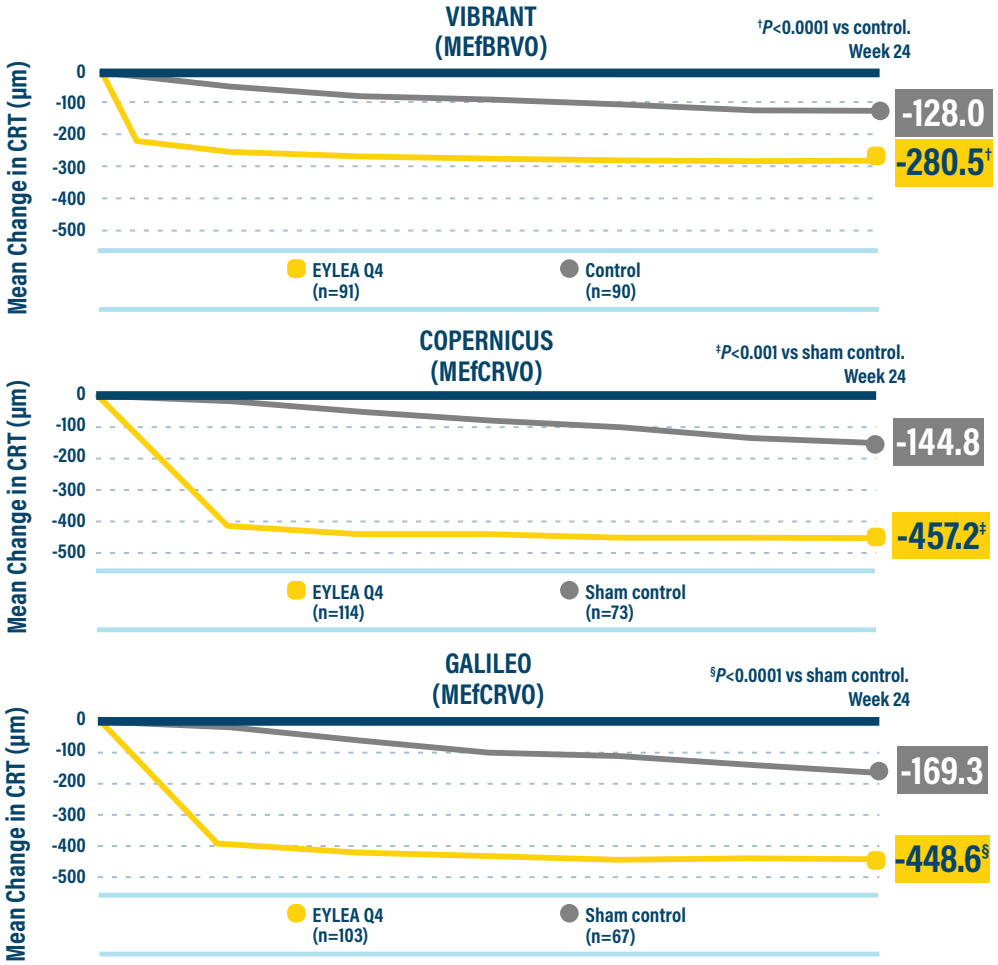

Figure 8: Mean change in CRT (µm) through 24 weeks (prespecified analyses)*

*Last observation carried forward; full analysis set.

Demonstrated safety profile

VIBRANT, COPERNICUS, and GALILEO demonstrated a consistent safety profile with EYLEA for patients with MEfRVO (Table 1). For patients with MEfBRVO, conjunctival hemorrhage and cataract occurred in ≥5% of patients. For those with MEfCRVO, eye pain, conjunctival hemorrhage, increased IOP, corneal epithelium defect, vitreous floaters, and ocular hyperemia were the most common adverse reactions occurring in ≥5% of patients. Less common adverse reactions reported in <1% of patients treated with EYLEA in the MEfCRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis. There is a potential risk of arterial thromboembolic events (ATEs) with the use of anti-VEGF agents; there were no Antiplatelet Trialists' Collaboration–defined ATEs in patients treated with EYLEA in the first 6 months of the MEfRVO studies.[2]

In clinical trials, EYLEA has not been associated with immunogenicity. In the phase 3 wet AMD, MEfRVO, and DME trials, the pretreatment immunoreactivity to EYLEA ranged from 1% to 3% across treatment groups and remained the same after 24 to 100 weeks of treatment. Importantly, there were no significant differences in efficacy and safety between patients with or without immunoreactivity.[2]

SELECT IMPORTANT SAFETY INFORMATION

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.

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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

Table 1: VIBRANT, COPERNICUS, and GALILEO: Most common adverse reactions (≥1%)

Additionally, postmarketing safety data of EYLEA are consistent with clinical trial data and have shown no new safety concerns, including co-occurrence of retinal artery occlusion (RAO) or retinal vasculitis with intraocular inflammation (IOI). Events of occlusive retinal vasculitis (ORV) and RAO in the context of IOI represent severe forms of inflammatory response and are considered sight-threatening conditions. In the EYLEA clinical trial data, which represent 8 pivotal trials in over 3000 patients, there were no reports of IOI with RAO or retinal vasculitis in eyes treated with EYLEA. After analyzing data from the EYLEA global safety database, which were based on 34 million doses sold, 6 cases describing RAO or retinal vasculitis with IOI were identified. These events have occurred at a rate of <1 per 6 million injections (0.00002%) and were all associated with endophthalmitis, indicating that ORV is not a safety concern with EYLEA.[5]

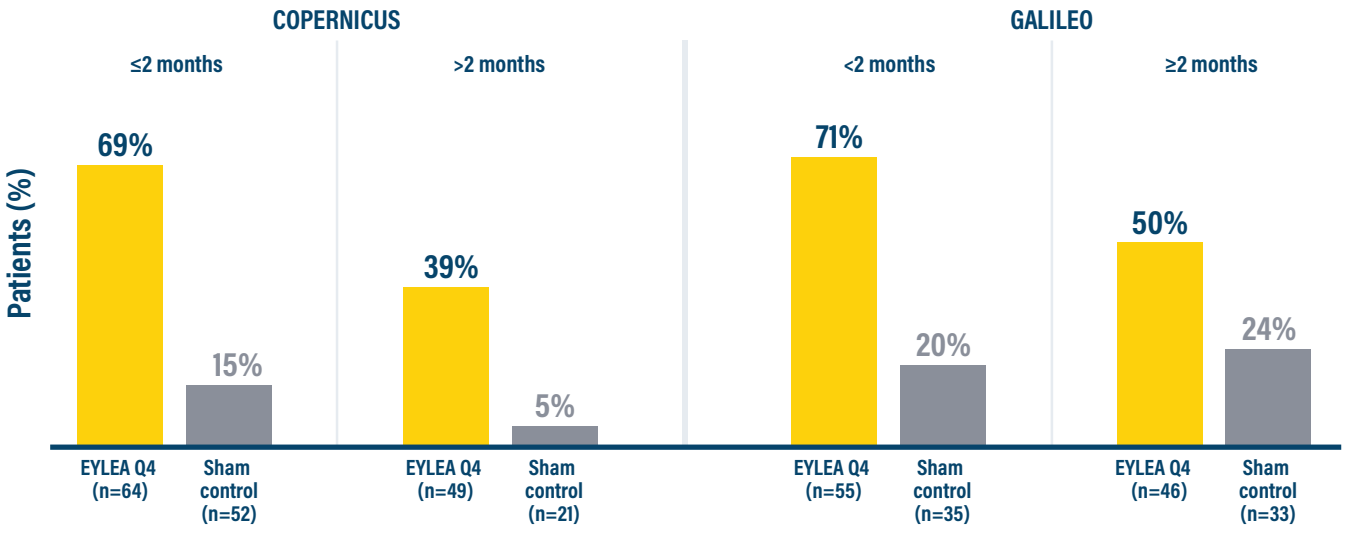

Figure 9: Percentage of patients who gained ≥15 ETDRS letters at 24 weeks by time to treatment (protocol-specified subgroup analysis)[II]

[II]Last observation carried forward; full analysis set.

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Summary

The approval of EYLEA in the treatment of MEfRVO introduced a pharmacologic option that binds VEGF and PlGF in a stable inactive complex.[2,4] The unique molecular characteristics of EYLEA allow it to inhibit a key step in the pathogenesis of MEfRVO, as it can bind all isoforms of VEGF in a 1:1 ratio to break the vicious cycle of VEGF-mediated damage in the eye.[4,24] Additionally, EYLEA can bind PlGF, which is upregulated in MEfRVO and is likely to work with VEGF to promote neovascularization and macular edema.[3,22,62,63]

The clinical effects of these distinct molecular characteristics are shown in the pivotal trials of EYLEA in the treatment of MEfRVO. EYLEA was evaluated in the VIBRANT, COPERNICUS, and GALILEO trials and was shown to have a clinically significant effect on visual and anatomic outcomes. The majority of patients treated with EYLEA in each trial had a significant VA improvement of ≥15 letters at week 24—with the vast majority of patients successfully keeping a VA at least at or better than baseline. Treatment with EYLEA also resulted in a significant reduction in CRT at week 24 in these trials.[6-8]

Additionally, patients treated with EYLEA benefited from vision gains regardless of baseline perfusion status.[7,64] Along with these efficacy results, EYLEA has shown a demonstrated safety profile across all indications, including MEfRVO. This safety profile is consistent with the EYLEA postmarketing safety data.[2,5] 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.

Given its powerful efficacy results demonstrated in pivotal trials, EYLEA is a powerful treatment option for patients diagnosed with MEfRVO. Eye care professionals should treat appropriate patients early with EYLEA to achieve sustained visual and anatomic improvements.

Acknowledgment

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SELECT IMPORTANT SAFETY INFORMATION

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.

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www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125387Orig1s043ltr.pdf
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REGENERON

EYLEA® (aflibercept) Injection
For Intravitreal Injection

777 Old Saw Mill River Road, Tarrytown, NY 10591

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 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), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR).

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 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.

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 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 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 intraocular pressure increased.

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).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

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

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	**EYLEA (N=1824)**	**Active Control (ranibizumab) (N=595)**	**EYLEA (N=1824)**	**Control (ranibizumab) (N=595)**
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

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 with a monthly 2 mg dose in 218 patients following central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT).

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

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

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

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). 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.

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

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	**EYLEA (N=578)**	**Control (N=287)**	**EYLEA (N=578)**	**Control (N=287)**
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

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, 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, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was 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.

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.

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:
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777 Old Saw Mill River Road
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Based on the August 2019
EYLEA® (aflibercept) Injection full
Prescribing Information.

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