Subject: Eylea (aflibercept)	**Original Effective Date:** 7/11/2014
Policy Number: MCP-191	**Revision Date(s):** 10/11/2016;
Review Date(s): 12/16/2015, 10/11/2016, 6/22/2017, 9/19/2017, 7/10/2018	
MCPC Approval Date: 7/10/2018	**P&T Approval Date:**

DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage policy (MCP) document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION STATEMENTS

This policy only addresses the FDA approved indications of Eylea (aflibercept) [neovascular (wet) AMD, diabetic macular edema (*including diabetic retinopathy in individuals with macular edema*), and macular edema following retinal vein occlusion (RVO) (*including central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO*)] when appropriate criteria are met.

The intent of this policy, Eylea (aflibercept), is to encourage the appropriate selection of preferred therapeutic agents for patients with AMD as supported by product labeling, clinical studies and clinical guidelines and positive therapeutic outcomes.

All other uses of Eylea (aflibercept) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

- Aflibercept has been studied in a population of patients who have not received prior anti-VEGF therapy for ARMD. In these populations, aflibercept (Eylea) was shown to be comparable to ranibizumab (Lucentis). Therefore, the response rate for aflibercept in patients who have been previously treated with anti-VEGF therapy is unknown.

- There are no published randomized, double-blind trials comparing aflibercept to other therapies in neovascular AMD.

- Clinical trials of aflibercept (Eylea) and other intravitreal VEGF inhibitors in the treatment of wet age-related macular degeneration have shown evidence of efficacy for maintaining or improving visual acuity; however, there is insufficient evidence to determine that one product is superior to another for efficacy or safety. Bevacizumab (Avastin) is the best value VEGF inhibitor for the treatment of ocular conditions.

PREFERRED AGENT: Avastin (bevacizumab)

Avastin (bevacizumab) is the preferred agent for the treatment of AMD and documentation of the failure of Avastin is required prior to authorization of with Eylea (aflibercept).

- There is no evidence to support the use of one VEGF-Inhibitor over another as the clinical trials provided data that showed comparability, none showed superiority. Results from the CATT research group indicate that bevacizumab and ranibizumab have equivalent effects on visual acuity for the treatment of ARMD when administered according to the same schedule.[1]

- Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF).[i] VEGF is the major angiogenic stimulus responsible for the formation of choroidal neovascularization and so represents a new paradigm in the treatment of retinovascular disease. Bevacizumab is FDA-approved for intravenous use in the treatment of metastatic colorectal, metastatic breast, and non-small cell lung cancer.
  - Bevacizumab was investigated first as a systemic intravenous treatment for AMD and then as an intravitreal injection (1.25 mg) before the FDA approved ranibizumab.[C (23,24)]
  - Based on published reports and compelling evidence of bevacizumab's safety and efficacy for use in a number of ophthalmic conditions, intravitreal bevacizumab is increasingly being administered as an off-label treatment in the United States and has been used in the treatment of the following off-label conditions that have not responded to other accepted therapies, including:[35]
    - *Neovascular (wet) age-related macular degeneration*
    - *Diabetic macular edema*
    - *Central retinal vein occlusion*
    - *Venous tributary (branch) occlusion*
    - *Proliferative diabetic retinopathy*
    - *Neovascular glaucoma; Adjunct*
  - Comparative trials and uncontrolled case series reported improvements in visual acuity and decreased retinal thickness by OCT (Optical Coherence Tomography) following intravitreal bevacizumab treatment.[C(25-31)]

- The off-label use of intravitreal bevacizumab as compared with ranibizumab was suggested to represent a highly cost-effective, off-label option for management of neovascular AMD.[22]
  Eylea (aflibercept), Macugen (pegaptanib), Lucentis (ranibizumab) are indicated for the treatment of neovascular age-related macular degeneration.
  - Intravitreal injection of bevacizumab has been used for the treatment of **neovascular age-related macular degeneration** (AHFS 2016).[h(1,8,9,10,11,12)] Results of several randomized controlled studies suggest that intravitreal bevacizumab has similar efficacy as ranibizumab in improving visual acuity.[1,10,11,12] In one study, the incidence of serious systemic adverse effects (primarily hospitalizations) appeared to be higher with bevacizumab compared with ranibizumab;[1] however, other studies, including a systematic review of 9 randomized controlled studies, directly comparing intravitreal injections of bevacizumab and ranibizumab in patients with neovascular age-related macular degeneration have found no such difference.[10,11]
  - Intravitreal injection of bevacizumab also has been used for the treatment of **diabetic macular edema** (AHFS 2016).[b(13,14,15)] Results of a study comparing intravitreal ranibizumab, aflibercept, and bevacizumab for the treatment of diabetic macular edema suggest that the relative treatment effect of these drugs may be dependent upon a patient's baseline visual acuity.[16,17] Further study is required to establish the role of bevacizumab in the treatment of diabetic macular edema.[13]
  - In the Comparison of AMD Treatment Trial (CATT), 1185 patients with wet AMD were randomly assigned to one of four groups: intravitreal injections of bevacizumab (1.25 mg) or ranibizumab (0.5 mg), with either drug given either monthly or as needed.[2] A meta-analysis combining results from one-year data of the CATT

trial[1] and two-year data from the IVAN trial found that bevacizumab was non-inferior to ranibizumab for visual acuity; additional randomized trials comparing the two drugs at two years also demonstrated non-inferiority for bevacizumab or equivalent efficacy.[34]

- Bevacizumab, in a 2-year randomized controlled trial, demonstrated similar mean gain of letters (8.6) as trials evaluating ranibizumab and is available at a fraction of the cost. [38]
- A 2013 cost-effectiveness analysis noted that despite variations in the study design and protocols of trials evaluating the anti-VEGF agents for DME, the mean letter improvement (approximately 9) is consistent across trials of the individual agents.[37] The analysis concluded the following: "insurers and health policymakers should consider endorsing the use of intravitreal bevacizumab over other treatment options as first-line therapy for CSDME (clinically significant DME) because this may curtail some of the rapidly increasing costs of managing patients with this condition."

- **The American Academy of Ophthalmology (AAO)** supports the use of intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab and ranibizumab) is the most effective way to manage neovascular AMD and represents the first-line of treatment.[E] AAO supports the use of bevacizumab for treatment of age-related macular degeneration as a recommendation with high importance to clinical care.[D,G]

In a letter to the Centers for Medicare and Medicaid Services (CMS) in April 2006[F], the AAO stated that "*It supports reimbursement for treating age-related macular degeneration (AMD) with intravitreal injections of bevacizumab, to meet the medical needs of many patients who have not responded to therapy with ocular photodynamic therapy (OPT) with verteporfin or intravitreal pegaptanib*". The letter also stated that "*intravitreal bevacizumab, sold under the brand Avastin, is being used by "a large number of retinal specialists (who) believe that it is reasonable and medically necessary for treatment of some patients with neovascular AMD.*" The Academy advised that while "*the scientific studies related to the use of intravitreal injections of bevacizumab for the treatment of neovascular AMD are supportive*," they are "*not conclusive of its safety and efficacy*." The AAO's support for coverage is limited to "*such patients who are deemed by their treating physician to have failed FDA-approved therapies, or in the judgment of their treating physician, based on his/her experience, are likely to have greater benefit from the use of intravitreal bevacizumab."*

CLASSIFICATION: An Ophthalmic Agent and a Vascular Endothelial Growth Factor (VEGF) inhibitor

FDA INDICATIONS

Eylea (aflibercept) is a VEGF inhibitor/solution for intravitreal injection indicated for the treatment of:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD): Treatment of neovascular (wet) age-related macular degeneration.

- Macular Edema Following Retinal Vein Occlusion (RVO): Treatment of macular edema following retinal vein occlusion.

- Diabetic Macular Edema (DME): Treatment of diabetic macular edema.

- Diabetic Retinopathy (DR) in Patients with Diabetic Macular Edema (DME): Treatment of diabetic retinopathy in patients with diabetic macular edema.

Available as: *Single-use, glass vial 40 mg/mL (2 mg/0.05 mL) solution for intravitreal injection*

Approved by the FDA:

- *Neovascular (Wet) Age-Related Macular Degeneration (AMD): 2011*
- *Macular Edema following Central Retinal Vein Occlusion (CRVO): 2012*

- *Macular Edema Following Retinal Vein Occlusion (BRVO and CRVO): 2014*
- *Diabetic Macular Edema (DME): 2014*

RECOMMENDATIONS/COVERAGE CRITERIA

Eylea (aflibercept) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❑ Board-certified ophthalmologist or retinal specialist

2. Diagnosis/Indication [ONE]

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

- ❒ Macular Edema Following Retinal Vein Occlusion (RVO) **[ONE]**
  - ❍ Macular edema from branch retinal vein occlusion
  - ❍ Macular edema from central retinal vein occlusion

- ❒ Diabetic Macular Edema (DME)

- ❒ Diabetic retinopathy (DR) associated with diabetic macular edema (DME)

3. Age/Gender/Other restrictions [ALL]

- ❑ 18 years of age or older[a-f]
  - ➢ *The safety and effectiveness of aflibercept in pediatric patients have not been established*.

4. Step/Conservative Therapy/Other condition Requirements [ALL]

- ❒ Insufficiently responsive (defined as 1-2 injections with minimal to no improvement) clinically significant adverse effects, or contraindication to **Avastin (bevacizumab).** Prescriber submit documentation of contraindication, adverse events, or date(s) of failed therapy
  EXCEPTION: Members with diagnosis of Diabetic Macular Edema (DME) and visual acuity less than 69 (Snellen equivalent 20/50 or worse) do **NOT** have to meet this criterion.[c,17]

- ❒ Eylea is prescribed as monotherapy (no other anti-VEGF medications)

5. Contraindications/Exclusions/Discontinuations to Eylea (aflibercept) therapy
Authorization will <u>not</u> be granted if ANY of the following conditions apply [ANY]
- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to aflibercept or any of the excipients in aflibercept
- ❒ Less than 18 years of age
- ❒ Ocular or periocular infections
- ❒ Active intraocular inflammation

- ❒ Prescribed for use in combination with other VEGF inhibitors, including but not limited to bevacizumab (Avastin), pegaptanib (Macugen), and ranibizumab (Lucentis)

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP are included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Eylea (aflibercept) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria

- ❑ Member currently meets ALL initial coverage criteria
- ❑ Subsequent authorizations will require the Member re-assessment for this condition to determine if continuation of treatment with requested medication is medically necessary. Clinical documentation indicating must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Condition Requirements

- ❑ Member displays improvement in disease state defined as stabilization of pre-treatment vision status or decreased progression of vision loss
- ❑ Compliance to treatment schedule as verified by Prescriber
  NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

3. Labs/Reports/Documentation required [ALL]

Eylea (aflibercept) maintenance therapy may be authorized when therapy has demonstrated efficacy as evidenced by an improvement in disease activity after initial therapy. Documentation of **disease stabilization or improvement** is required for continuation of therapy.

- ❒ Evidence of treatment efficacy as documented of ONE (1) of the following compared to baseline: [ONE]
  - ❍ Detained neovascularization
  - ❍ Clinical improvement or stability with visual acuity
  - ❍ Maintenance of corrected visual acuity from prior treatment
- ❒ Examination identifying evidence of retinal cysts and/or subretinal fluid (hemorrhage by OCT or fluorescein angiography[G, 19] (as applicable). Prescriber submit documentation of exam/diagnostic test results if completed.
- ❒ Persistent evidence of lesion activity, however the lesion continues to respond to repeated treatment
- ❒ Administration of intravitreal therapy (*recorded in the procedure or post-procedure note following the completion of treatments*) for the previous authorization period with the following information: name of the medication, dose/amount of drug administered, and treated eye (Right eye, Left eye, or Both eyes)

4. Discontinuation of Treatment

Member should be assessed for discontinuation of therapy if **ANY** of the following are applicable: **[ANY]**

- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms following the initial authorization of coverage
- ❑ Absence of unacceptable toxicity from the drug (i.e. endophthalmitis and retinal detachments; increase in intraocular pressure; arterial thromboembolic events)
- ❒ Deterioration of eye visual acuity to less than 20/320 in the eye being treated after three or more injections
- ❒ Reduction of best corrected visual acuity (BCVA) in the treated eye to less than 15 letters (3 Snellen lines), on 2 consecutive visits in the treated eye, attributed to wet AMD in the absence of other pathology
- ❒ Deterioration of lesion morphology despite optimal treatment as evidenced by worsening of optical coherence tomography (OCT), increase of lesion size or other evidence of disease activity resulting from new hemorrhage or exudates over 3 consecutive visits
- ❒ Examination identifies a fluid free macula
- ❑ Contraindications/Exclusions to Eylea (aflibercept) therapy

  Authorization will <u>not</u> be granted if ANY of the following conditions apply [ANY]
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to aflibercept or any of the excipients in aflibercept
  - ❍ Less than 18 years of age
  - ❍ Ocular or periocular infections
  - ❍ Active intraocular inflammation
  - ❍ Prescribed for use in combination with other VEGF inhibitors, including but not limited to bevacizumab (Avastin), pegaptanib (Macugen), and ranibizumab (Lucentis)

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

1. Recommended Dosage [ONE]

INDICATION	DOSE
Neovascular (Wet) Age-Related Macular Degeneration (AMD)	Initiation: 2 mg (0.05 mL) intravitreally once every 4 weeks (monthly) per eye for the first 3 months Maintenance: 2 mg (0.05 mL) once every 8 weeks (2 months); however Eylea may be dosed as frequently as 2 mg every 4 weeks (monthly) † *†Although Eylea may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when Eylea was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).*
Macular Edema following Retinal Vein Occlusion (RVO) [CRVO/BRVO]	2 mg (0.05 mL) intravitreally once every 4 weeks (monthly) per eye
Diabetic Macular Edema (DME) **Diabetic Retinopathy with DME**	Initiation: 2 mg (0.05 mL) intravitreally once every 4 weeks (monthly) per eye for the first 5 injections† Maintenance: 2 mg (0.05 mL) once every 8 weeks (2 months); however Eylea may be dosed as frequently as 2 mg every 4 weeks (monthly)† *†Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).*

NOTE: Bevacizumab is not currently packaged and prepared by the manufacturer in doses appropriate for intravitreal injection. Physicians routinely obtain single doses prepared by qualified compounding pharmacies to minimize risk of contamination of the injected drug.

2. Authorization Limit [ALL]

- ❑ Quantity limit: 2 mg intravitreally once a month per eye [2 mg injection = 1 vial per month] **AND** ONE OF THE FOLLOWING AS APPLICABLE: [ONE]

  - ❍ **Neovascular (Wet) Age-Related Macular Degeneration (AMD)**
    - 2mg (per eye) every 4 weeks for first 3 doses; 2mg (per eye) every 8 weeks thereafter
    - 2mg (per eye) every 4 weeks chronically may be considered on a case-by-case basis depending on individual's initial response to every 8 week maintenance dosing. Prescriber submit supporting documentation for Medical/Pharmacy Director review.

- ❍ **Macular Edema following Retinal Vein Occlusion (RVO) [CRVO/BRVO]:** 2mg (per eye) every 4 weeks

- ❍ **Diabetic Macular Edema (DME)**
  - 2mg (per eye) every 4 weeks for the first 5 doses; 2mg (per eye) every 8 weeks thereafter
  - 2mg (per eye) every 4 weeks chronically may be considered on a case-by-case basis depending on individual's initial response to every 8 week maintenance dosing. Prescriber submit supporting documentation for Medical/Pharmacy Director review.

❒ Duration of initial authorization: **3 months**

❒ Continuation of treatment: Re-authorization for continuation of treatment is required every **6 months** to determine continued need based on member meeting 'Continuation of Therapy' criteria

3. Route of Administration [ALL]

❑ Aflibercept (Eylea) is considered to be **provider-administered** by intravitreal injection by a retinal specialist.

❑ Provider-administration will be authorized in a **physician office** setting only. Routine administration in a hospital or outpatient setting will not be authorized.

❑ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.

COVERAGE EXCLUSIONS

This policy only addresses the indication of Eylea (aflibercept) when appropriate criteria are met.

All other uses of Eylea (aflibercept) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

SUMMARY

Eylea (aflibercept) is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

Age-Related Macular Degeneration (AMD)

AMD is an eye disease characterized by progressive degeneration of the macula, the central part of the retina at the back of the eye. When this is caused by the development of abnormal blood vessels develop behind the retina, the condition is commonly referred to as "wet" or neovascular AMD. These new blood vessels tend to be fragile and leak blood and fluid. The blood and fluid raise the macula from its normal position at the back of the eye. With wet AMD, loss of central vision can occur quickly. AMD is the leading cause of severe vision loss in people over 55 years of age in the developed world. The neovascular "wet" form of this disease represents 10% of the overall disease prevalence but is responsible for roughly 90% of the vision loss due to AMD. It is more common in Caucasians and its incidence increases with age as it is estimated that 10 to 15% of individuals older than 80 years have some form of AMD.

- On November 18, 2011 the FDA approved aflibercept for the treatment of individuals with neovascular "wet" AMD. Heier and colleagues (2012) reported on two phase-III studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD [VIEW 1, VIEW 2]) in which participants were treated and evaluated for efficacy of aflibercept versus ranibizumab.

  - The 2 pivotal trials for this drug are reported in the product labeling.[3,4]
    - It was concluded that after 52 weeks of treatment, aflibercept intravitreal 2 mg every 8 weeks (following 3 initial monthly doses) was clinically equivalent to ranibizumab intravitreal 0.5 mg every 4 weeks for maintaining visual acuity in patients with neovascular AMD.
    - After treatment for 12 months, aflibercept (labeled regimen) prevented loss of visual acuity in 94 – 95% of patients and improved visual acuity in 31% of patients compared to baseline.
  - The FDA's approval of Eylea® was based on positive results from the two phase-3 studies [VIEW 1, VIEW 2: **V**EGF Trap-Eye: **I**nvestigation of **E**fficacy and Safety in **W**et AMD (VIEW) trials reported by Heier and colleagues (2012) evaluated for efficacy of aflibercept versus ranibizumab.[3,4]
    - The efficacy of EYLEA was demonstrated by 52-week results in 2 randomized, multicenter, double-masked, active-controlled studies (VIEW 1 and VIEW 2) involving 2419 patients with Wet AMD.

- A total of 2457 patients with all 3 subtypes of AMD (occult, minimally classic, predominantly classic) were enrolled in the 2 studies. VIEW1 was conducted primarily in North America and VIEW2 was conducted primarily in Europe, Asia, Australia, and Latin America. Both trials used a non-inferiority design with a 10% margin and tested doses of aflibercept.
- The participants were randomly assigned to one of 4 treatment arms with 3 of the treatment arms receiving varying doses of aflibercept and 1 treatment arm receiving ranibizumab (n=2419; mean age, 76 years; range, 49 to 99 years).
- The primary outcome measure in the phase III trials was the proportion of patients that maintained vision at week 52. Maintenance of vision was defined as a loss of fewer than 15 letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score compared to baseline.
- Intravitreal aflibercept was dosed monthly or every 2 months after 3 initial monthly doses showed similar efficacy and safety outcomes as the monthly doses of ranibizumab.
- The groups who received intravitreal aflibercept had best corrected visual acuity within 0.5 letters of the ranibizumab group. Side effects were similar among the treatment groups.
- Summary: Eylea was found to be as effective as the VEGF inhibitor ranibizumab (Lucentis®, Genentech/Roche) in two clinical trials involving 2,457 adults.
  - In VIEW1 evaluated at 52 weeks: The proportion of patients who maintained visual acuity (less than 15 letter loss of best corrected visual acuity (BCVA) from baseline; primary outcome) was 94% (aflibercept 8-week arm) and 94% (ranibizumab 4-week arm). The treatment difference at 52 weeks between aflibercept every 8 weeks and ranibizumab was 0.6 letters (95.1% confidence interval, -3.2 to 4.4 letters).
  - In VIEW2 evaluated at 52 weeks: The proportion of patients who maintained visual acuity was 95% among all treatment arms. The treatment difference at 52 weeks between aflibercept every 8 weeks and ranibizumab was 0.6 (95.1% CI, -2.9 to 4 letters).
  - The proportion of patients who gained at least 15 letters of vision from baseline was similar for aflibercept 8-week and ranibizumab in VIEW1 (31% and 31%, respectively) and in VIEW2 (31% and 34%, respectively). The mean change in BCVA (Early Treatment Diabetic Retinopathy Study) was also similar among all arms in VIEW1 and VIEW2

➢ Safety

- Most common Adverse Events (AEs) reported with aflibercept include conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, IOP increase
- Treatment-related AEs were noted to be similar between aflibercept and ranibizumab in the comparative trials

❖ The **Comparison of AMD Treatment Trials (CATT)** was a multicenter clinical trial that compared the safety and effectiveness of bevacizumab to ranibizumab and an individualized dosing regimen (as-needed, or PRN) to monthly injections. **At one year, the CATT study found that ranibizumab and bevacizumab had comparable equivalence visual acuity improvements for monthly dosing.**[1] Ranibizumab PRN had non-inferior visual acuity improvements compared with a fixed schedule of monthly injections. Further follow-up at two years showed that the two drugs remained comparable in both efficacy and safety but the PRN arms together did not perform as well in terms of maintaining the visual gains at the end of year one compared with the two monthly injection arms, especially in the bevacizumab PRN group.[19]

Similar results were seen in the 2-year **Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN)** trial conducted in the United Kingdom.[20,21] [*Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN trial):* This study compared intravitreal bevacizumab to ranibizumab dosed either on a continuous (monthly) or discontinuous (PRN) basis. It was a 2-year study conducted in the United Kingdom.] Currently, there does not appear to be a significant difference in efficacy between ranibizumab and bevacizumab. The systemic safety data in the CATT and IVAN studies are inconclusive.

The CATT trial[1] and a meta-analysis of the CATT and IVAN trials[21], however, showed a small reduction in vision compared with monthly treatment, although the difference was likely not clinically significant.[35,36] Additionally, the CATT trial found an increase in mortality in patients receiving discontinuous, rather than monthly, injections, and raises safety concerns with intermittent dosing.[21]

Comparison of AMD Treatment Trials (CATT)[1]

A multi-center, single-blind, non-inferiority study was conducted by the CATT Research Group in 1,185 patients with neovascular AMD. Participants were randomly assigned to receive intravitreal injections of either ranibizumab or bevacizumab on a monthly schedule or as needed with monthly evaluations. Patients with wet AMD were randomly assigned to one of four groups: intravitreal injections of bevacizumab (1.25 mg) or ranibizumab (0.5 mg), with either drug given either monthly or as needed.

- The primary outcome of the study was the mean change in visual acuity at one year, with a non-inferiority limit of 5 letters on the eye chart.
- The investigators reported that monthly administration of bevacizumab was equivalent to monthly administration of ranibizumab, with 8.0 and 8.5 letters gained, respectively. Results of as needed administration of the agents were determined to be equivalent, with bevacizumab recipients gaining 5.9 letters and ranibizumab recipients gaining 6.8 letters.
- Ranibizumab as needed was equivalent to monthly ranibizumab, while the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm, p=0.03 by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either treatment (p>0.20). However, the proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern. Therefore, the investigators recommended that differences in rates of serious adverse events should be further studied.
- Summary: The primary outcome was the mean change in visual acuity at 1 year, with a non-inferiority limit of 5 letters on the eye chart. Bevacizumab administered monthly was equivalent to ranibizumab administered monthly. Bevacizumab administered as needed was equivalent to ranibizumab as needed. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. **At one year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly.**

Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN)[20,21]

The IVAN, enrolled 610 patients and found that for the primary outcome of best visual acuity at two years, bevacizumab was neither noninferior nor inferior to ranibizumab. **There was no difference in mortality, atherothrombotic events, or hospital admission between the two drugs. A meta-analysis combining results from one-year data of the CATT trial and two-year data from the IVAN trial found that bevacizumab was noninferior to ranibizumab for visual acuity**;[21] additional randomized trials comparing the two drugs at two years also demonstrated noninferiority for bevacizumab[28] or equivalent efficacy.[34]

❖ **Cochrane Database of Systematic Reviews:** Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. (Aug 2014)

Solomon et al. (Cochrane Review, 2014) conducted a review to investigate the ocular and systemic effects of, and quality of life associated with, intravitreally injected anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) for the treatment of neovascular AMD compared with no anti-VEGF treatment. A database search identified 12 randomized controlled trials which included 5496 patients with neovascular AMD. All trials followed participants for at least one year.

The review also evaluated the relative effects of one anti-VEGF agent compared with another when administered in comparable dosages and regimens. The authors included randomized controlled trials (RCTs) that evaluated pegaptanib, ranibizumab, or bevacizumab versus each other or a control treatment (e.g., sham treatment or photodynamic therapy). The ocular and systemic effects of, and quality of life associated with, intravitreally injected anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) for the treatment of neovascular AMD compared with no anti-VEGF treatment; and the relative effects of one anti-VEGF agent compared with another when administered in comparable dosages and regimens.[18]

- One trial compared pegaptanib, three trials ranibizumab, and two trials bevacizumab versus controls; six trials compared bevacizumab with ranibizumab. Four trials were conducted by pharmaceutical companies; none of the eight studies which evaluated bevacizumab were funded by pharmaceutical companies. The trials were conducted at various centers across five continents (North and South America, Europe, Asia and Australia).
- The overall quality of the evidence was very good, with most trials having an overall low risk of bias.
- Results
    - When compared with control treatments, participants who received any of the three anti-VEGF agents were more likely to have gained 15 letters or more of visual acuity, lost fewer than 15 letters of visual acuity, and had vision 20/200 or better after one year of follow up.
    - **Visual acuity outcomes after bevacizumab and ranibizumab were similar when the same regimens were compared in the same RCTs, despite the substantially lower cost for bevacizumab compared with ranibizumab.**
    - **No trial directly compared pegaptanib with other anti-VEGF agents; however, when compared with controls, ranibizumab or bevacizumab yielded larger improvements in visual acuity outcomes than pegaptanib.**
    - Participants treated with anti-VEGFs showed improvements in morphologic outcomes (e.g., size of CNV or central retinal thickness) compared with participants not treated with anti-VEGF agents.
    - There was less reduction in central retinal thickness among bevacizumab-treated participants than among ranibizumab-treated participants after one year (MD -13.97 μm; 95% confidence interval (CI) -26.52 to -1.41); however, this difference is within the range of measurement error and we did not interpret it as being clinically meaningful.
- Adverse Events
    - Inflammation and increased pressure in the eye were the most common vision-related adverse events with anti-VEGF agents. Endophthalmitis was reported in < 1% of anti-VEGF-treated patients and no cases were reported in control groups. The occurrence of serious adverse health effects, such as high blood pressure and internal bleeding, was comparable across anti-VEGF-treated groups and control groups; however, the number of events was small relative to the number of people in the studies making it difficult to detect any meaningful differences between groups. Few data were available for visual function (e.g., reading speed and critical print size), quality of life, and economic outcomes.
    - The occurrence of serious systemic adverse events was comparable across anti-VEGF-treated groups and control groups; however, the numbers of events and trial participants may have been insufficient to detect a meaningful difference between groups. Data for visual function, quality of life, and economic outcomes were sparsely measured and reported.
- Conclusion: Results of this review indicate the effectiveness of anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) in terms of maintaining visual acuity; ranibizumab and bevacizumab were also shown to improve visual acuity. The information available on the adverse effects of each medication do not suggest a higher incidence of potentially vision-threatening complications with intravitreal injection compared with control interventions; however, clinical trial sample sizes may not have been sufficient to detect rare safety outcomes.

Macular Edema and Central Retinal Vein Occlusion

The FDA approved aflibercept for the treatment of macular edema following CRVO in September 2012. The approval was based on two randomized, multi-center, double-masked, sham-controlled studies in individuals with macular edema following CRVO.

Safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, sham-controlled studies (COPERNICUS and GALILEO) in patients with Macular Edema following CRVO. The study authors evaluated the long-term effects of Eylea over both six- and 12-month treatment intervals. In both studies, the primary endpoint was to achieve a visual gain of 15 or more ETDRS letters (equivalent to a three-line gain on the Snellen chart).[a]

- A total of 358 patients were enrolled in COPERNICUS and GALILEO. Of these, 217 were dosed with Eylea and the remaining 141 subjects received sham injections. In both studies, 2mg Eylea injections were administered monthly for the first six months and then as needed for the subsequent six months.
- The same was true for the sham treatment group in COPERNICUS; however, subjects in the sham arm of GALILEO received monthly injections for an entire year.
- At the six-month follow-up in COPERNICUS, 56.1% of patients who received Eylea gained at least 15 ETDRS letters from baseline acuity compared to just 12.3% of patients who had sham injections.[5,a] Patients who were treated with Eylea gained an average of 17.3 ETDRS letters, which correlated with decreased macular thickness.[5,a] Additionally, just 3.5% of patients who received Eylea experienced adverse events (e.g., conjunctival hemorrhage, reduced visual acuity and ocular pain) vs. 13.5% of patients who received sham injections.[5,a]
- Patients in GALILEO experienced similar results. After six months, 60.2% of patients who were treated with Eylea gained 15 ETDRS letters versus 22% of patients who received sham injections.[a] Further, patients in the treatment group achieved an average visual acuity gain of 18 ETDRS letters.[a]
- At the one-year follow-up, patients in both studies who received Eylea exhibited comparable visual improvement levels to those documented at six months. However, approximately 30% of patients in both studies who received sham injections achieved a 15-letter gain after one year of placebo therapy.[6]

<u>COPERNICUS</u>

The published study, Boyer and colleagues (2012), reported on the 6 month results of the phase 3 Vascular Endothelial Growth Factor [VEGF] Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion [CRVO] (COPERNICUS). [5]

- This study enrolled 189 eyes with macular edema secondary to CRVO.
- The primary endpoint was the number of eyes with a gain of 15 letters or more in best corrected visual acuity from baseline to week 24. Participants were randomly assigned in a 3:2 ratio to receive either receive aflibercept (n=115 eyes) or sham injections (n=74 eyes) every 4 weeks for 24 weeks. Assessments were performed on day 1, at week 4, and every 4 weeks thereafter to week 24.
- Assessments included a full ocular exam, visual acuity testing, slit-lamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure measurement and optical coherence tomography. Examiners were masked to treatment assignment. The National Eye Institute 25-item Visual Function Questionnaire was administered at baseline and at week 24.
- Clinical Endpoints[a,5]
    - Primary Endpoint: Proportion of patients who gained at least 15 letters in Best Corrected Visual Acuity (BCVA) from baseline to 24 weeks as measured by Early Treatment Diabetic Retinopathy Study (ETDRS)
    - Key Secondary Endpoint: Mean change in BCVA as measured by ETDRS letter score from baseline to 24 weeks
- At the 24 week assessment, 110 participants in the aflibercept group remained and 60 participants in the sham group remained.
- The aflibercept group had a mean gain of 17.3 ± 12.8 letters at 24 weeks compared with a mean loss of 4.0 ± 18.0 letters in the sham group. At week 24, the aflibercept group showed an improvement of 7.2 points in the National Eye

Institute 25-item Visual Function Questionnaire total score compared to an improvement of 0.8 points in the sham group. Visual acuity maintained throughout the course of the 24-week study.

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

Diabetic retinopathy is a common microvascular complication of diabetes and a major cause of visual impairment in adults. Among patients with diabetic retinopathy, development of diabetic macular edema (DME) is the leading cause of vision loss. Of the available anti-VEGF therapies, ranibizumab and aflibercept are FDA approved for DME. While there are randomized controlled trial data supporting ranibizumab, intravitreal bevacizumab also has evidence demonstrating similar efficacy and safety, however on a smaller scale.

- While no direct comparisons of anti-VEGF therapy are available, bevacizumab, in a 2-year randomized controlled trial, demonstrated similar mean gain of letters (8.6) as trials evaluating ranibizumab with a good cost-effective profile in the management of DME
- A 2013 cost-effectiveness analysis noted that despite variations in the study design and protocols of trials evaluating the anti-VEGF agents for DME, the mean letter improvement (approximately 9) is consistent across trials of the individual agents.[37] The analysis concluded the following: "*insurers and health policymakers should consider endorsing the use of intravitreal bevacizumab over other treatment options as first-line therapy for CSDME (clinically significant DME) because this may curtail some of the rapidly increasing costs of managing patients with this condition".*

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Diabetic Macular Edema (DME)

In July 2014, the FDA approved aflibercept for the treatment of diabetic macular edema. The evidence on treatment of DME with aflibercept includes a double-masked multi-center phase 2 RCT and 2 double-masked multicenter phase 3 RCTs.[a,32] The control in all 3 trials was laser photocoagulation.

- DA VINCI was a phase 2 multi-center (39 sites) trial of aflibercept (called VEGF Trap- Eye in the study) compared with laser photocoagulation. A total of 221 patients with DME were randomized to 1 of 5 treatment regimens: 0.5-mg aflibercept every 4 weeks; 2-mg aflibercept every 4 weeks; 2-mg aflibercept for 3 initial monthly doses and then every 8 weeks; 2-mg aflibercept for 3 initial monthly doses and then on an as-needed (PRN) basis; or macular laser photocoagulation. Gains from baseline of ≥15 letters were seen in 21% in the laser group. In the aflibercept groups, gains from baseline of ≥15 letters ranged from 17% to 34%. Outcomes tended to be worse for the 0.5 mg and the 8-week interval groups. No patients in the 2-mg aflibercept groups lost 15 or more letters compared with 9.1% of the laser group. Gains in visual acuity were significantly greater in the aflibercept groups (from 8.5 to 11.4 letters) compared with the laser group (2.5 letters).
- Two-year results from the pivotal phase 3 trials (VIVID-DME, VISTA-DME) were published in 2015.[32] A total of 872 eyes from 127 sites world-wide were randomized to 1 of 2 dosing regimens (2 mg every 4 weeks or 2 mg every 8 weeks) or to laser photocoagulation. Rescue treatment with aflibercept or laser was allowed after 24 weeks. At 1-year, eyes treated with aflibercept gained a mean of 10.5 to 12.5 letters (4 groups), compared with 0.2 and 1.2 letters for the 2 laser groups. At 2-years, eyes treated with aflibercept gained a mean of 9.4 to 11.5 letters compared to 0.8 letters with laser. About one-third of patients in the aflibercept groups gained at least 15 letters, compared with about 12.5% of the photocoagulation group.

Bevacizumab (PREFERRED): Diabetic Macular Edema

Improvement in visual acuity letter score (range, 0 to 100, with higher scores indicating better visual acuity; a score of 85 is approximately 20/20) at 1 year in patients with center-involved diabetic macular edema was seen in the aflibercept, bevacizumab, and ranibizumab treatments groups with no significant difference between groups (13.3 vs 9.7 vs 11.2) in a randomized trial (N=660).

- The mean number of injections was 9 in aflibercept, 10 in bevacizumab, and 10 in ranibizumab groups.
- In subgroup analysis, when the initial visual acuity letter score was 78 to 69 (Snellen equivalent, 20/32 to 20/40), there was no significant between groups in the mean improvement in letter score from baseline. In this subgroup,

there was a significant decrease in central subfield thickness for aflibercept compared with bevacizumab (-129 vs -67 mcm) and for ranibizumab compared with bevacizumab (-119 vs -67 mcm) but the difference was not significant for aflibercept compared with ranibizumab.

- When the initial visual acuity letter score was less than 69 (Snellen equivalent 20/50 or worse) the mean improvement in letter score was significant for aflibercept compared with bevacizumab (18.9 vs 11.8) and for aflibercept compared with ranibizumab (18.9 vs 14.2), but was not significant for ranibizumab compared with bevacizumab (14.2 vs 11.8). In this subgroup, there was a significant decrease in central subfield thickness for aflibercept compared with bevacizumab (-210 vs -135 mcm) and for ranibizumab compared with bevacizumab (-176 vs -135 mcm) but the difference was not significant for aflibercept compared with ranibizumab.[17]

PLoS (Public Library of Science) compared the efficacy and safety of current treatments in diabetic macular edema (DME).[39]

- PubMed, Embase, and CENTRAL were systematically reviewed for randomized controlled trials of current treatments in DME through August 2015. Data on the mean change of best-corrected visual acuity (BCVA) and central macular thickness (CMT) were extracted, and adverse events (AEs) were collected. A total of 21 trials were included in the network meta-analysis.
- Intravitreal ranibizumab improved BCVA most significantly (OR: +7.01 95% CI [confidence interval] [2.56 to 11.39]) in 6 months and intravitreal aflibercept (+8.19 (5.07 to 11.96)) in 12 months.
- Intravitreal triamcinolone combined with LASER decreased CMT most significantly (-111.34 (-254.61 to 37.93)) in 6 months and intravitreal aflibercept (-110.83 (-190.25 to -35.27)) in 12 months.
- Compared with the relatively high rate of ocular AEs in the groups with administration of steroids, systematic AEs occurred more frequently in the groups with vascular endothelial growth factor inhibitors involved.
- The analysis confirms that intravitreal aflibercept is most favorable with both BCVA improvement and CMT decrease than other current therapies in the management of DME within 12 months.

Diabetic Retinopathy

As summarized in FDA-approved prescribing information, the pivotal phase 3 trials (VIVID, VISTA, described before) evaluated the change in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS).[a] All 862 patients that were evaluated had diabetic retinopathy and macular edema at baseline. At 100 weeks, about 1/3 of patients in the aflibercept groups gained at least 2 steps in the ETDRS-DRSS compared with 7% of controls in VIVID and 16% of controls in VISTA.

❖ **Diabetic Retinopathy Clinical Research Network (DRCRN)** in a 2015 study reported on the 1-year outcome of safety and efficacy of a head-to-head comparison of aflibercept, bevacizumab and ranibizumab in the treatment of DME.

Individuals were randomized to receive either aflibercept (n=224), bevacizumab (n=218) or ranibizumab (n=218). During the first year, visits occurred every 4 weeks. Each visit involved best-corrected visual acuity (as measured by ETDRS) and optical coherence tomography to measure central subfield thickness.

- In the aflibercept group, the mean improvement in the visual acuity letter score was 13.3 and the central subfield thickness decreased by 169±138 μm.
- In the bevacizumab group the mean improvement in visual acuity letter score was 9.7 with a central subfield thickness decrease of 101±121 μm.
- In the ranibizumab group the mean improvement in visual acuity letter score was 11.2 with a decreased central subfield thickness of 147±134 μm.
- Although the participants who received aflibercept showed a greater improvement in visual acuity, the difference was driven by the eyes with the worse visual acuity at baseline. For the participants with an initial visual-acuity letter score of 78 to 69, 20 participants had a mean improvement of 8.0 with aflibercept, 7.5 with bevacizumab, and 8.3 with ranibizumab. For the participants with an initial letter score less than 69, the mean improvement was 18.9 with aflibercept, 11.8 with bevacizumab, and 14.2 with ranibizumab.

- Adverse events included 2 participants who received aflibercept and ranibizumab with injection-related infectious endophthalmitis (both nonstudy eyes).
- While the injections improved vision, there were no differences among the groups if the initial visual acuity loss was mild; aflibercept was more effective at improving vision if the initial visual acuity levels were worse.

PRACTICE GUIDELINES AND POSITION STATEMENTS

❖ **American Academy of Ophthalmology (AAO): Age-Related Macular Degeneration Preferred Practice Patterns (2014)**

The following recommendations for the care of AMD:

- Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (eg, aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
- Intravitreal anti-VEGF therapy is generally well-tolerated and rarely associated with serious adverse events such as infectious endophthalmitis or retinal detachment. Symptoms suggestive of postinjection endophthalmitis or retinal detachment require prompt evaluation.

❖ **American Academy of Ophthalmology (AAO) Retina/Vitreous Panel: Diabetic Retinopathy Preferred Practice Pattern (2016)**

The AAO 2016 Preferred Practice Pattern (PPP) for diabetic retinopathy concludes that intravitreal injection of anti-VEGF agents is the initial treatment of choice for center-involving diabetic macular edema.[A] Laser photocoagulation remains the preferred treatment for non-center-involving diabetic macular edema. The panel concluded that VEGF antagonists are an alternative for proliferative diabetic retinopathy, and when it is at the high-risk stage (i.e., if new vessels at the optic disc is extensive or vitreous/preretinal hemorrhage has occurred recently), anti-VEGF therapy and panretinal photocoagulation may be performed concomitantly. The PPP indicates that anti-VEGF therapy for the management of severe non-proliferative diabetic retinopathy and non-high-risk proliferative diabetic retinopathy is being evaluated.

❖ **American Academy of Ophthalmology (AAO) Retina/Vitreous Panel: Retinal Vein Occlusions Preferred Practice Pattern Guidelines (2015)**

AAO 2015 Preferred Practice Pattern (PPP) for retinal vein occlusions states that the safest treatment for macular edema associated with CRVOs and BRVOs is anti-VEGF treatment.[B] This is based on well conducted studies that have shown efficacy of anti-VEGF treatment for macular edema associated with CRVO and BRVO. The body of evidence was considered to be of good quality leading to a strong recommendation.

DEFINITIONS

Age-related macular degeneration (AMD) There are 2 forms of AMD: wet and dry. The dry form is the most common form and is characterized by yellow deposits in the retina, called “drusen”. The dry form can progress to the wet form, which is more aggressive and severe. Wet or exudative AMD is caused by the growth of abnormal leaky blood vessels (choroidal neovascularization or CNV) that eventually damage the macula. The macula is the area of the eye responsible for central vision, which is essential for most visual activities, including reading, driving, and recognizing faces. CNV associated with wet AMD may include classic or occult neovascular leakage patterns. Classic CNV is distinct or well demarcated during fluorescein angiography whereas occult CNV is obscured or poorly demarcated on fluorescein angiography.

Branch retinal vein occlusion: An occlusion near the retina in a branch retinal vein.

Central retinal vein occlusion: An occlusion of the central retinal vein where it enters the eye.

Diabetic macular edema (DME): The leakage of fluid from retinal blood vessels which in turn causes the macula to swell.

Diabetic retinopathy (DR) : The progressive damage to the blood vessels in the back of the eye.

Neovascular glaucoma: A severe form of glaucoma with devastating visual outcome caused by the growth of new blood vessels which obstruct aqueous humor outflow.
Neovascularization: The formation of abnormal new blood vessels.

Retinal vein occlusion (RVO): A blockage of one or more veins that carry blood away from the retina. Central retinal vein occlusion (CRVO) occurs when the blockage is in the main vein in the retina. Branch retinal vein occlusion (BRVO) occurs when the blockage is one of the smaller veins attached to the main vein in the retina.

Retinopathy: Damage to the retina.

Vascular endothelial growth factor (VEGF): A chemical signal produced by the body's cells that stimulates growth of new blood vessels.

CODING INFORMATION

CPT	Description
67028	Intravitreal injection of a pharmacologic agent (separate procedure)

HCPCS	Description
J0178	Injection, aflibercept, 1 mg
ICD-9	**Description [For dates of service prior to 10/01/2015]**
362.50	Degeneration of macula and posterior pole
362.51	Macular degeneration (senile), unspecified
362.52	Exudative senile macular degeneration

ICD-10	Description [For dates of service on or after 10/01/2015]
H35.30	Unspecified Macular Degeneration Age-related
H35.31	Nonexudative Age-Related Macular Degeneration
H35.32	Exudative Age-Related Macular Degeneration

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AMR Review: September 2016
Peer Reviewer Specialty: Board certified in Ophthalmology, Surgery Vitreoretina (CA)