| | |
|---|---|
| **Subject: Eylea (aflibercept)** | **Original Effective Date:** 7/11/2014 |
| **Policy Number:** MCP-191 | **Revision Date(s):** 10/11/2016; Q3 2019 |
| **MCP Review Date(s):** 12/16/2015, 10/11/2016, 6/22/2017, 9/19/2017, 7/10/2018; Q3 2020 | |
| **P&T Approval Date:** Q3 2019, Q3 2020 | |

## DISCLAIMER

*This Molina Clinical Policy (MCP) 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 MCP document and provide the directive for all Medicare members.*

Contents



## SUMMARY OF EVIDENCE/POSITION

This policy addresses the FDA approved indications of Eylea (aflibercept) 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) when appropriate criteria are met.

The information outlined in the Molina Clinical Policy includes, but is not limited to, a review of evidence-based information obtained from the following sources Evaluation of New and Existing Technologies (UM 10).

*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.

- Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). 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. [Michels S, et al. 2005; Avery RL, et al. 2006; AAO Retina/Vitreous Panel. Preferred Practice Pattern Guidelines. Age-Related Macular Degeneration.]
  - 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.

- Intravitreal injection of bevacizumab has been used for the treatment of **neovascular age-related macular degeneration** (AHFS 2019). Results of several randomized controlled studies suggest that intravitreal bevacizumab has similar efficacy as ranibizumab in improving visual acuity. In one study, the incidence of serious systemic adverse effects (primarily hospitalizations) appeared to be higher with bevacizumab compared with ranibizumab; 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.

- Intravitreal injection of bevacizumab also has been used for the treatment of **diabetic macular edema** (AHFS 2019). 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 (Wells JA, et al). Further study is required to establish the role of bevacizumab in the treatment of diabetic macular edema (Mitchell P et. al 2014).

- 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.
    - 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 PRN was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive.
    - 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. (Martin DF, et al. 2012)
    - **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 Study Investigators 2012, 2013]
  The IVAN enrolled 610 patients and found that for the primary outcome of best visual acuity at two years, bevacizumab was neither non-inferior 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 non-inferior to ranibizumab for visual acuity**; additional randomized trials comparing the two drugs at two years also demonstrated non-inferiority for bevacizumab (Kodjikian L, et al. 2013) or equivalent efficacy (Berg K, et al. 2016)

- **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. AAO supports the use of bevacizumab for treatment of age-related macular degeneration as a recommendation with high importance to clinical care.

In a letter to the Centers for Medicare and Medicaid Services (CMS) in April 2006, 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."*

## 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): Treatment of diabetic retinopathy

Available as: Single-dose vial and pre-filled syringe: 2 mg/0.05 mL solution

Approved by the FDA:
- Neovascular (Wet) Age-Related Macular Degeneration (AMD): Nov 2011
- Macular Edema following Retinal Vein Occlusion (RVO): Sep 2012
- Diabetic Macular Edema (DME): July 2014
- Expanded indication: Diabetic retinopathy in patients with DME: March 2015
- Diabetic retinopathy: May 2019

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

## COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

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)
  **NOTE:** DME indicated by the presence of clinically significant macular edema as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS): Retinal thickening within 500 micrometers (µm) of the center of the fovea, OR Hard exudates within 500 µm (≤ 500 micrometers) of the fovea center with adjacent retinal thickening, OR At least 1 disc area of retinal thickening, any part of which is within 1 disc diameter of the center of the fovea *Fraser CE*

- ❒ Diabetic retinopathy (DR)

**3. Age/Gender/Other restrictions [ALL]**

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

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

- ❒ Inadequate response (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 to Avastin (bevacizumab).

  **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.

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

5. **Contraindications/Exclusions/Discontinuations to Eylea (aflibercept) therapy**
   Authorization will not 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.

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

**1. Initial Coverage Criteria**

- ❑ Reauthorization request is for the **same eye** as initial authorization
  **NOTE:** The continuation of therapy criteria is only for the same previously treated eye. If member has developed condition in an untreated eye, Prescriber must submit new request with 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. 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.

- ❒ Response to treatment (including disease progression or history of progressive visual loss or worsening of anatomic appearance) as determined by fluorescein angiography, Optical Coherence Tomography (OCT) or Scanning Computerized Ophthalmic Diagnostic Imaging (SCODI) 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 (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)

**3. 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 not 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

*Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.*

### 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<br><br>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) †<br><br>*†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)**<br><br>AND<br><br>**Diabetic Retinopathy** | Initiation: 2 mg (0.05 mL) intravitreally once every 4 weeks (monthly) per eye for the first 5 injections†<br><br>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)†<br><br>*†Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4-week (monthly) dosing after the first 20 weeks (5 months).* |

### 2. Authorization Limit [ALL]

- ❑ Quantity limit: **2 mg intravitreally once a month per eye** [2 mg injection = 1 vial per month]
- ❑ 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 **provider-administered** via 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.
- ❑ Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11
- ❑ 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.*

## BACKGROUND/SUMMARY

**Eylea (aflibercept)**
Aflibercept is a recombinant fusion protein that acts as a decoy receptor for vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PLGF). Aflibercept binds to VEGF-A and PLGF and inhibits binding and activating of endothelial cell receptors, thereby suppressing neovascularization and slowing vision loss.

### Age-Related Macular Degeneration (AMD)

On November 18, 2011 the FDA approved aflibercept for the treatment of individuals with neovascular "wet" AMD. 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. (Heier JS, et al. 2012)

- 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 (Heier JS, et al. 2012; Schmidt-Erfurth U, et al. 2014).
- 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.
- 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

- **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
    - The 2 pivotal trials for this drug are reported in the product labeling.
        - 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.

**MetaAnalysis/Systematic Reviews**

- A 2016 Cochrane Review examined outcomes comparing **aflibercept versus ranibizumab** injections in over 2400 patients with neovascular AMD, from two randomized controlled trials. Both treatment options yielded similar improvements in visual acuity and morphological outcomes in patients, though the authors note that the aflibercept treatment regimen has the potential to reduce treatment burden other risks from injections. (Sarwar S, et al. 2016)

  Current available information on adverse effects of each medication suggests that the safety profile of aflibercept is comparable with that of ranibizumab; however, the number of participants who experienced adverse events was small, leading to imprecise estimates of absolute and relative effect sizes. The eight-week dosing regimen of aflibercept represents reduced treatment requirements in comparison with monthly dosing regimens and thus has the potential to reduce treatment burden and risks associated with frequent injections. There was no clinical trial that compared aflibercept versus bevacizumab for the treatment of individuals with neovascular AMD (Sarwar et al. 2016). Several studies have compared ranibizumab versus bevacizumab for outcomes of neovascular AMD (Solomon 2014).

**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) (Boyer D, et al. 2012)

- 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. Patients who were treated with Eylea gained an average of 17.3 ETDRS letters, which correlated with decreased macular thickness. 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.
- 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. Further, patients in the treatment group achieved an average visual acuity gain of 18 ETDRS letters.
- 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. (Figueroa MS, et al. 2012)

COPERNICUS

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).

- 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
  - 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.

***S***tudy of ***CO***mparative Treatments for ***RE***tinal Vein Occlusion 2 (SCORE2)
A clinical trial funded by the National Eye Institute (NEI), part of the National Institutes of Health evaluated the head-to-head comparative safety and efficacy of Avastin (bevacizumab) and Eylea (aflibercept)

- Phase III prospective multicenter randomized clinical trial designed to assess whether intravitreal bevacizumab is non-inferior to intravitreal aflibercept for treatment of decreased vision attributable to macular edema due to central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO)
- In addition, SCORE2 compared monthly dosing to treat-and-extend dosing of aflibercept or bevacizumab from 6 to 12 months with respect to visual acuity and central retinal thickness at month 12 in participants who had a protocol-defined good response after six monthly injections of aflibercept or bevacizumab.
- 362 participants, including 307 with CRVO and 55 with HRVO
- Study eyes were randomized 1:1 to intravitreal bevacizumab (1.25 mg) every four weeks for six months vs. intravitreal aflibercept (2 mg) every 4 weeks for 6 months
- At six months, visual acuity, retinal thickness, and adverse effects were assessed
- Results:
    - SCORE2 results, show that average visual acuity in both groups improved about four lines on an eye chart, from about 20/100 visual acuity to 20/40 visual acuity.
    - SCORE2 participants with macular edema due to CRVO or HRVO, intravitreal bevacizumab was non-inferior to intravitreal aflibercept with respect to visual acuity after six months of treatment, based on a non-inferiority margin of a VALS of five. Both groups demonstrated significant decreases in CST from baseline to month six, with no significant difference between the groups with respect to the magnitude of CST reduction.
    - Of note, the proportion of eyes that achieved resolution of macular edema at month six was significantly lower in the bevacizumab group than in the aflibercept group. While this difference was not associated with a difference between study groups in visual acuity outcomes at month six, continued follow-up of SCORE2 participants will allow evaluation of the cumulative effect of the presence of fluid on visual acuity and on the number of injections administered in participants assigned to the treatment groups not defined by a fixed-dosing schedule.
    - Ongoing follow-up will also provide information regarding longer-term outcomes, including visual acuity, need for continuing treatment, development of complications of CRVO and HRVO, quality of life and morphologic outcomes.

**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. The control in all 3 trials was laser photocoagulation. (Brown DM, et al. 2015)

- 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. 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 (Brown DM, et al. 2015).

**EXPANDED INDICATION:** On March 25, 2015, the FDA approved an expanded indication for Eylea (aflibercept) injection to treat diabetic retinopathy in patients with diabetic macular edema.

- The safety and efficacy of the expanded indication were demonstrated in two clinical trials involving 679 patients with diabetic retinopathy and diabetic macular edema. The participants received either aflibercept or macular laser photocoagulation. At week 100, participants who were treated with aflibercept showed significant improvement in the severity of their diabetic retinopathy, compared with participants in the other group.
- The injection is administered by a physician once per month for the first five injections and then once every 2 months. It is intended to be prescribed along with appropriate interventions to control blood glucose, blood pressure, and cholesterol.

**Bevacizumab (PREFERRED): Diabetic Macular Edema (DME)**

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 DME 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 (Wells JA, et al. 2016)

PLoS (Public Library of Science) compared the efficacy and safety of current treatments in DME (PLoS 2016)

- Bevacizumab, ranibizumab, and aflibercept for treating macular edema due to RVO 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.

  Anti-vascular endothelial growth factor for diabetic macular edema: a network meta-analysis [Cochrane Database Syst Rev. 2017]
  The 2014 update of this review found high-quality evidence of benefit with anti-VEGF modalities, compared to laser photocoagulation, for the treatment of DME. The review compared the relative efficacy and safety of the three most commonly used drugs as interventions of direct interest for practice: aflibercept and ranibizumab, used on-label; and off-label bevacizumab.

  This 2017 review update evaluated the effects of anti-VEGF drugs on DME found that while all three studied treatments have advantages over laser therapy, there was moderate evidence that aflibercept is significantly favored in all measured efficacy outcomes over ranibizumab and bevacizumab, after one year (Virgili G, et al. 2017).

  It was concluded that aflibercept may confer some advantage over ranibizumab and bevacizumab in people with DME at one year in visual and anatomic terms, however it is unclear whether this is applicable long-term. There were no indication of differences in overall safety between the three antiangiogenic drugs that are currently available to treat DME. More evidence on the long-term (greater than two years) comparative effects of these anti-VEGF agents is needed.

## Diabetic Retinopathy

**Diabetic retinopathy** (DR) 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

The FDA approval of Eylea as a treatment for DR was based on 6-month and 1-year results from PANORAMA, a randomized, multi-center, controlled Phase 3 trial that enrolled 402 patients and was designed to investigate Eylea for the improvement of moderately severe to severe non-proliferative diabetic retinopathy (NPDR) without DME, compared to sham injection. PANORAMA is the first prospective trial to study whether an anti-VEGF can also help prevent worsening disease in patients with NPDR without DME.
Details on trial design included:

- Three treatment arms: An observational sham injection group and two Eylea treatment groups. Eylea was dosed every eight weeks (following five initial monthly doses) or every 16 weeks (following three initial monthly doses and one eight-week interval).
- Primary endpoint: The primary endpoint was the proportion of patients who experienced a two-step or greater improvement in the diabetic retinopathy severity scale (DRSS) from baseline for the combined Eylea treatment groups at week 24, and for each Eylea treatment group separately (every eight-week group and every 16-week group) at week 52. The DRSS is a systematic grading scale to assess DR severity based on photographs of the retina.

- Secondary endpoints: These included assessment of whether Eylea reduced the risk of worsening disease – specifically progression to PDR (including anterior segment neovascularization [ASNV]) or the development of center-involved DME – as well as change in visual acuity.
- Results: In the study, 58% of patients who were treated with Eylea achieved a two-step or greater improvement in Diabetic Retinopathy Severity Scale ("DRSS") score from baseline at week 24 compared with 6% of patients receiving sham injection.
- Results improved when the treatment was continued for a period of one year. The study showed that 80% and 65% of patients receiving Eylea every 8 weeks and 16 weeks, respectively, achieved two-step or greater improvement in DRSS compared to 15% for sham injection arm.
- The PANORAMA trial showed that by 1 year 20% of untreated patients developed proliferative diabetic eye disease, and Eylea reduced this risk by 85% to 88% when administered using an every 16-week or 8-week dosing regimen, respectively. In fact, 80% of patients who received the Eylea 8-week dosing regimen had significant improvement in their diabetic retinopathy.

## 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 (e.g., 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 post-injection 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. 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. 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): chemical signal produced by the body's cells that stimulates growth of new blood vessels.

**CODING INFORMATION:** THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

| CPT | Description |
|---|---|
| 67028 | Intravitreal injection of a pharmacologic agent (separate procedure)--Prior Authorization not required on this CPT code |

| HCPCS | Description |
|---|---|
| J0178 | Injection, aflibercept, 1 mg |

## REFERENCES

**Package Insert, FDA, Drug Compendia**

Eylea (aflibercept) [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals Inc; Aug 2019.

Avastin (bevacizumab) [prescribing information]. South San Francisco, CA: Genentech, Inc; June 2019.

American Hospital Formulary Service (AHFS). Drug Information 2019. [STAT!Ref Web site]. Available at: http://online.statref.com. [via subscription only]. Accessed April 2020.

Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at www.clinicalpharmacology.com. Accessed April 2020. [Available with subscription]

Drug Facts and Comparisons. Facts and Comparisons eAnswers [online]. Clinical Drug Information LLC, 2020. Available from Wolters Kluwer Health, Inc. Accessed April 2020. [Available with subscription]

Food and Drug Administration (FDA). FDA approves new treatment for diabetic retinopathy in patients with diabetic macular edema [news release]. March 25, 2015.

Regeneron Pharmaceuticals Inc. EYELEA® (aflibercept) Injection [prescribing information]. Revised March 2015. Food and Drug Administration [website].

ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited February 2019]. Available from: http://clinicaltrials.gov/.

**Clinical Trials, Definitions, Peer-Reviewed Publications**

Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Martin DF, Maguire MG et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011; 364:1897-908. [PubMed 21526923]

Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012 Jul;119(7):1388-98.

IVAN Study Investigators, Chakravarthy U, Harding SP et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology*. 2012; 119:1399-411. [PubMed 22578446]

IVAN Study Investigators, Chakravarthy U, Harding SP et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularization: 2-year findings of the IVAN randomized controlled trial. *Lancet*. 2013; 382:1258-67..

Chakravarthy U, Harding SP, Rogers CA et al. A randomized controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularization (IVAN). *Health Technol Assess*. 2015; 19:1-298.

Heier JS, Brown DM, Chong V et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012; 119:2537-48. [PubMed 23084240]

Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology 2014; 121:193.

Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the Phase 3 COPERNICUS Study. Ophthalmology. 2012;119:1024-1032.

Figueroa MS, Contreras I. Potential anti-vascular endothelial growth factor therapies for central retinal vein occlusion. Drugs. 2012 Nov 12;72(16):2063-71.

Arroyo, JG. Age-related macular degeneration: Treatment and prevention. In: **UpToDate,** Trobe, J (Ed), **UpToDate,** Waltham, MA, 2019. Accessed June 2019.

Tufail A, Patel PJ, Egan C, et al, ABC Trial Investigators. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicenter randomised double masked study. BMJ 2010;340:c2459.

Mitchell P, Wong TY, Diabetic Macular Edema Treatment Guideline Working Group. Management paradigms for **diabetic macular edema.** Am J Ophthalmol. 2014; 157:505-13.e1-8. [PubMed 24269850]

Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015; 372:1193-203. [PubMed 25692915]

Wells JA, Glassman AR, et al.: Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology 2016;123:1351-1359.

Patel JJ, Mendes MA, et al. Cost-utility analysis of bevacizumab versus ranibizumab in neovascular age-related macular degeneration using a Markov model. J Eval Clin Pract 2012;18:247-55.

Michels S, Rosenfeld PJ, et al. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. Ophthalmology 2005;112:1035-47.

Avery RL, Pieramici DJ, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 2006;113:363-72.

Bashshur ZF, Haddad ZA, Schakal A, et al. Intravitreal bevacizumab for treatment of neovascular age-related macular degeneration: a one-year prospective study. Am J Ophthalmol 2008;145:249-56.

Arevalo JF, Sanchez JG, Wu L, et al, Pan-American Collaborative Retina Study Group. Intravitreal bevacizumab for subfoveal choroidal neovascularization in age-related macular degeneration at twenty-four months: the Pan-American Collaborative Retina Study. Ophthalmology 2010;117:1974-81.

Lai TY, Liu DT, et al. Visual outcomes and growth factor changes of two dosages of intravitreal bevacizumab for neovascular age-related macular degeneration: a randomized, controlled trial. Retina 2009;29:1218-26.

Kodjikian L, Souied EH, et al. Ranibizumab versus Bevacizumab for Neovascular Age-related Macular Degeneration: Results from the GEFAL Noninferiority Randomized Trial. Ophthalmology 2013; 120:2300.

Modarres M, Naseripour M, et al. Intravitreal injection of 2.5 mg versus 1.25 mg bevacizumab (Avastin) for treatment of CNV associated with AMD. Retina 2009;29:319-24.

Subramanian ML, Abedi G, Ness S, et al. Bevacizumab vs ranibizumab for age-related macular degeneration: 1-year outcomes of a prospective, double-masked randomized clinical trial. Eye (Lond) 2010;24:1708-15.

Brown DM, Schmidt-Erfurth U, Do DV et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology*. 2015; 122:2044-52. [PubMed 26198808]

Korobelnik JF, Do DV, Schmidt-Erfurth U et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology*. 2014; 121:2247-54. [PubMed 25012934]

Berg K, Hadzalic E, Gjertsen I, et al. Ranibizumab or Bevacizumab for Neovascular Age-Related Macular Degeneration According to the Lucentis Compared to Avastin Study Treat-and-Extend Protocol: Two-Year Results. Ophthalmology 2016; 123:51.

Rajendram R, Fraser-Bell S, Kaines A et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of **diabetic macular edema**: 24-month data: report 3. Arch Ophthalmol. 2012; 130:972-9. [PubMed 22491395]

PLoS One. 2016 Jul 19;11(7):e0159553. doi: 10.1371/journal.pone.0159553. eCollection 2016. The Efficacy and Safety of Current Treatments in Diabetic Macular Edema: A Systematic Review and Network Meta-Analysis.

Moja L, Lucenteforte E, Kwag KH et al. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. **Cochrane Database of Systematic Reviews** 2014; 9:CD011230. [PubMed 25220133]

Solomon SD, Lindsley K, et al. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. **Cochrane Database of Systematic Reviews** 2014 Aug 29;8:CD005139.
**Update:** Solomon SD, Lindsley K, et al. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. **Cochrane Database of Systematic Reviews** 2019, 3: CD005139. DOI: 10.1002/14651858.CD005139.pub4.

Sarwar S, Clearfield E, et al. Aflibercept for neovascular age-related macular degeneration. **Cochrane Database of Systematic Reviews** 2016. 2: CD011346. doi:10.1002/14651858.CD011346.pub2. PMC 5030844. PMID 26857947.

Virgili G, Parravano M, Evans JR, Gordon I, Lucenteforte E. Anti-vascular endothelial growth factor for diabetic macular edema: a network meta-analysis. **Cochrane Database of Systematic Reviews** 2018, 10: CD007419. DOI: 10.1002/14651858.CD007419.pub6.

Scott IU, VanVeldhuisen PC, Ip MS, et al, for the SCORE Investigator Group. SCORE2 Report 2: Study design and baseline characteristics. Ophthalmology. 2017;124:245-256.

Scott IU, VanVeldhuisen PC, Ip MS, et al, for the SCORE2 Investigator Group. Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion. The SCORE2 randomized clinical trial. JAMA 2017:317:2072-2087.

Scott IU, VanVeldhuisen PC, Ip MS, et al, for the SCORE2 Investigator Group. SCORE2 Study Report 4. Baseline factors associated with 6-month visual acuity and retinal thickness outcomes in patients with macular edema secondary to central retinal vein occlusion or hemiretinal vein occlusion. JAMA Ophthalmol 2017;135:639-649

**Government Agencies, Professional Societies, and Other Authoritative Publications**

American Society of Retinal Specialists Bevacizumab Position Paper. American Society of Retinal Specialists; 2008 June.

American Academy of Ophthalmology (AAO)

American Academy of Ophthalmology Retina/Vitreous Panel.

- **Diabetic Retinopathy** Preferred Practice Pattern. February 2016
- **Retinal Vein Occlusions** Preferred Practice Pattern Guidelines. November 2015
- Practice Pattern Guidelines. **Age-Related Macular Degeneration.** San Francisco, CA: American Academy of Ophthalmology; January 2015.

American Academy of Ophthalmology Supports Coverage of Ophthalmologists' Use of Intravitreal Bevacizumab. AAO Press Release describing its letter to the Centers for Medicare and Medicaid Services available at: www.aao.org.

Ophthalmologists Say Medicare Physician Payment Data Needs More Clarity to Benefit the Public. Available at: http://www.aao.org/newsroom/news-releases/detail/ophthalmologists-say-medicare-physician-payment-da

| Policy History | Approval |
|---|---|
| Policy Developed<br>Peer Review: Diana Cokingtin, MD | MCPC<br>9/17/2014 |
| Revision<br>Peer Review: AMR Peer Review Network. 9/20/2016. Practicing Physician. Board certified in Board certified in Ophthalmology, Surgery Vitreoretina (CA) | MCPC<br>12/14/2016 |
| Revision<br>Peer Review: AMR Peer Review Network. 7/1/2019. Practicing Physician. Board certified in Ophthalmology (CA)<br>Notable revisions: Diabetic Retinopathy (DR) indication and applicable criterion and content added. | P&T<br>Q3 2019 |
| Annual Review*<br>No coverage criteria changes with this annual review. Minor revisions, including clarification and addition of language, however no change to intent.<br>Notable update: Added newly approved pre-filled syringe dosage form. | P&T<br>Q3 2020 |

*NOTE: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Revisions.' Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer. The revisions noted below but may not be all-inclusive of all revised criteria and content in each policy; refer to MCP for all revisions and complete context.