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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 Centers for Medicare and Medicaid Services (CMS). 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.

The intent of the policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical studies, nationally recognized authoritative references, and current peer-reviewed scientific literature. 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. The information outlined in the MCP 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). This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

RECOMMENDATION

This policy addresses the FDA approved indications of Eylea (aflibercept) for the treatment of patients with neovascular age-related macular degeneration, macular edema following retinal vein occlusion, diabetic macular edema, and diabetic retinopathy when appropriate criteria are met.

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.

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Age-related macular degeneration (AMD) is characterized by progressive degeneration of the macula, the central part of the retina, leading to central vision loss. Central vision loss caused by AMD is the leading cause of blindness among the elderly in developed countries. AMD is characterized as either dry (atrophic or non-neovascular) or wet (exudative or neovascular). Dry AMD accounts for about 90% of AMD cases but only 10% of AMD-related vision loss (AAO 2019). Neovascular (wet) AMD is characterized by choroidal neovascularization (CNV) or growth of abnormal vessels into the subretinal space. These abnormal blood vessels leak leading to collections of subretinal fluid and/or blood beneath the retina. Growth of new blood vessels in patients with neovascular AMD is driven by a complex process that involves a signal protein called vascular endothelial growth factor A (VEGF-A). VEGF, through its promotion of angiogenesis and vascular permeability, is a central component of the pathologic process driving wet AMD, as well as other choroidal and retinal vascular disorders. The goals of anti-VEGF therapy in neovascular AMD are to achieve functional visual acuity and maintain a dry macula on clinical and OCT examination. Intravitreal anti-VEGF drugs are generally first-line treatment for neovascular AMD due to their potential to cause robust improvements in vision; they are much more effective in this outcome compared with older treatment options such as photodynamic therapy (AAO 2019; Bakri et al. 2019; Schmidt-Erfurth et al. 2014; Tuuminen et al. 2017). **Treatment decisions in neovascular AMD are informed by the results of comparative trials among anti-VEGF agents** (Heier et al. 2012; Bakri et al. 2019; Dugel et al. 2020; Kodjikian et al. 2013; CATT Research Group; IVAN Study Investigators).

Diabetic retinopathy (DR) is a common progressive, microvascular complication of diabetes in which retinal vascular damage and abnormalities can lead to vision impairment and is a major cause of visual impairment in adults. Diabetes results in vasoconstriction, which upregulates VEGF expression. VEGF increases retinal vascular permeability, causes breakdown of the blood-retina barrier, and results in retina edema (Stewart 2012). VEGF is up-regulated in diabetic macular edema and proliferative DR. Among patients with DR, development of DME is the leading cause of vision loss. DR can be classified based on disease severity: 1) Non-proliferative DR characterized by retinal vascular abnormalities; 2) Proliferative DR characterized by retinal neovascularization in addition to vascular abnormalities; and 3) DME characterized by thickening of the retina near the macula.

Diabetic macular edema (DME) is a complication of DR caused by fluid accumulation in the macula, or central portion of the eye, that causes the macula to swell. DME can be present in all stages of DR and is the most common cause of vision loss in patients with DR with an increasing prevalence tied to type 2 diabetes mellitus. Management recommendations for patients with diabetes are described according to severity of the retinopathy

as well as the presence and type of DME (AA0 2019). DME is classified as either center-involved (CI-DME) or noncenter-involved DME (NCI-DME). Multiple, high quality clinical trials have demonstrated that anti-VEGF therapy is more effective in improving vision in CI-DME than monotherapy with focal laser treatment, supplanting it as the first-line therapy (AAO 2019). Intravitreal anti-VEGF therapy is indicated for proliferative DR and DME with central involvement. VEGF-inhibitors is generally recommended as initial therapy in most patients with DME and impaired visual acuity. Of the available anti-VEGF therapies, ranibizumab (Lucentis) and aflibercept (Eylea) are FDA approved for DME.

Retinal vein occlusion (RVO) is a blockage of a portion of the venous circulation that drains the retina and is classified according to where the occlusion is located. Pressure builds up in the capillaries and result in hemorrhage and leakage of fluid and blood which can lead to macular edema with leakage near the macula. 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. The prognosis of RVOs varies according to the site of the occlusion and the type of occlusion (ischemic or nonischemic). In general, more-distal RVOs with less occlusion have a better prognosis than more-proximal RVOs with greater ischemia. VEGF increases vessel permeability by increasing the phosphorylation of tight junction proteins and thus an important mediator of the blood-retinal barrier breakdown leading to vascular leakage and macular edema (EURETINA 2019). Therefore, therapy that inhibits VEGF is an effective therapeutic modality targeting the underlying pathogenesis of macular edema. Anti-VEGF agents are commonly used to treat the macular edema, reduce the severity of anterior segment neovascularization, and lower the risk of ocular angiogenesis (AAO 2019). Anti-VEGF intravitreal therapy has become the standard of care for management of macular edema due to RVO.

Eylea (aflibercept injection), a recombinant humanized fusion protein, is a vascular endothelial growth factor A (VEGF-A) and placental growth factor (PlGF) antagonist. Aflibercept acts as a soluble decoy receptor that binds to VEGF-A and PlGF and inhibits their biologic activity. VEGF-A induces neovascularization (angiogenesis) and increases vascular permeability, which appear to play a role in the pathogenesis and progression of the neovascular (wet) form of AMD, macular edema following retinal vein occlusion, diabetic macular edema, and diabetic retinopathy. Binding of aflibercept to VEGF-A and PlGF prevents these factors from binding to endogenous VEGF receptors, reducing neovascularization and vascular permeability. Eylea is indicated for the treatment of neovascular (wet) AMD, Macular Edema following RVO, DME, and DR.

FDA INDICATIONS

FDA-approved indication does not alone 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.

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

Diabetic macular edema (DME): Treatment of diabetic macular edema

Diabetic Retinopathy (DR): Treatment of diabetic retinopathy

Macular Edema: Treatment of macular edema following retinal vein occlusion (RVO)

Available as: single-use vial kit or single-use pre-filled syringe (2 mg/0.05 mL solution)

FDA Approval:
- Neovascular (Wet) AMD: Nov 2011
- Macular Edema following RVO: Sep 2012
- DME: July 2014
- DR in patients with DME: March 2015
- Diabetic retinopathy: May 2019

CLASSIFICATION: Ophthalmic Agent; VEGF Inhibitor

CENTERS FOR MEDICARE & MEDICAID SERVICES (CMS)

A National Coverage Determination (NCD) for the use of VEGF inhibitors [Avastin (bevacizumab), Eylea (aflibercept), Lucentis (ranibizumab) and Macugen (pegaptanib) was not identified. Local Coverage Determinations (LCDs)/ Local Coverage Articles (LCAs) may exist.

In a letter to the 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."*

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]**
   Documentation of ALL of the following criteria are required. May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information.

   ❒ 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).** Documentation of contraindication, adverse events, or date(s) of failed therapy to Avastin (bevacizumab) required.

   EXCEPTION: Members with diagnosis of Diabetic Macular Edema and baseline visual acuity of 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, [i.e. 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.

- ❒ Prescriber to maintain record of administration of intravitreal therapy (recorded in the procedure or post-procedure note following the completion of treatments) with the following information: name of the medication, dose/amount of drug administered, and treated eye (Right eye, Left eye, or Both eyes). Submit with re-authorization requests.

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

REAUTHORIZATION /CONTINUATION OF THERAPY

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

1. Reauthorization 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.

- ❒ Eylea prescribed as monotherapy: Member is not on additional anti-VEGF medications [i.e. bevacizumab (Avastin), pegaptanib (Macugen), and ranibizumab (Lucentis)]

- ❒ Subsequent authorizations require member re-assessment at least once annually for this condition to determine if continuation of treatment with requested medication is medically necessary. Prescriber submit clinical documentation of assessment.

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]
  - ❍ Reduction or maintenance of corrected visual acuity from prior treatment
  - ❍ Detained neovascularization
  - ❍ Clinical improvement or stability in best corrected visual acuity (BCVA) or visual field
  - ❍ Reduction or maintenance of corrected visual acuity from prior treatment
  - ❍ Supportive findings from optical coherence tomography or fluorescein angiography

- ❒ 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 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, [i.e. 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) 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 AND **Diabetic Retinopathy**	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).*

2. Authorization Limit [ALL]

- ❒ Quantity Limit
  - ❍ **2 mg intravitreally once a month per eye** [2 mg injection = 1 vial per month]
  - ❍ Members with an insufficient response during initial therapy administered every 4 weeks may continue with dosing every 4 weeks. Members with an inadequate response to maintenance therapy administered every 8 weeks may increase the dosing frequency up to every 4 weeks.
- ❒ 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. 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

All other uses of Eylea (aflibercept) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy is 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.

BACKGROUND/SUMMARY

Clinical trials of aflibercept and other intravitreal VEGF inhibitors in the treatment of wet AMD have shown evidence of efficacy for maintaining or improving visual acuity; however, **there is insufficient evidence to determine the superiority of one VEGF agent over the other. The evidence to support the use of one anti-VEGF therapy over another is scant as most of the clinical trials provided data demonstrating comparability, rather than superiority, in safety and efficacy.**

Several randomized control trials (RCTs) have been conducted to compare the effects of the frequently used anti-VEGF agents, ranibizumab and bevacizumab (Avastin), for the treatment of wet AMD since bevacizumab has not been FDA approved for intraocular injection and has been more cost-effective than ranibizumab. In addition, two RCTs available found that Avastin, Eylea, and Lucentis were all non-inferior to each other, and therefore, choice of treatment should be based on patient characteristics, side effect profiles, cost, and availability. However, a comparative effectiveness study demonstrated that aflibercept (Eylea) was on average, was more effective at improving vision in patients with a visual acuity of less than or equal to 20/50 (Wells et al. 2015); therefore, in such cases, bevacizumab (Avastin) is not recommended prior to Eylea.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted a comparative effectiveness trial comparing the three commonly used anti-VEGF agents [aflibercept (Eylea), bevacizumab (Avastin), and ranibizumab (Lucentis)] for center-involved DME associated with visual impairment (Well et al. 2015). All three agents were noted to improve vision, on average, with treatment group differences varying according to initial visual acuity in the previously reported 1-year results. No apparent differences in visual acuity, on average, were identified among the groups when baseline visual acuity impairment was mild (20/32 to 20/40); however, at lower levels of visual acuity (20/50 to 20/320), aflibercept was more effective at improving vision than the other two agents. No statistically significant differences in pre-specified ocular or systemic safety events among the 3 anti-VEGF agents were identified.

The comparative effectiveness study for center-involved DME demonstrated vision gains in all three drugs at the 2-year visit, with an average of almost half the number of injections, slightly decreased frequency of visits, and decreased amounts of focal/grid laser treatment in all 3 groups in the second year. Wells et al. (2016) concluded in a 2-year randomized trial for center-involved DME that all 3 anti-VEGF groups had vision improvements at 2 years with fewer injections. At 2 years, in eyes with better baseline visual acuity, there still were no meaningful differences identified in mean visual acuity change among the treatment groups. Visual acuity outcomes were similar among treatment groups for eyes with baseline VA 20/32 - 20/40. In eyes with baseline VA of 20/50 or worse (20/50 - 20/320), the advantage of aflibercept (Eylea) over ranibizumab (Lucentis), noted at 1 year, had decreased and was no longer statistically significant at 2 years. Aflibercept (Eylea) remained superior to bevacizumab (Avastin). Overall, few eyes in any group lost substantial amounts of vision, regardless of the baseline visual acuity. More APTC events with ranibizumab. Rates of ocular adverse events, including endophthalmitis and post-injection inflammation, remained low through 2 years with all 3 agents; however, systemic Anti-Platelet Trialists' Collaboration (APTC) events were higher in the ranibizumab group over two years justifies continued evaluation in future studies.

A systematic review evaluated the effectiveness and safety of intravitreal injections of aflibercept versus ranibizumab, bevacizumab, or sham for treatment of patients with neovascular AMD from two RCTs (total of 2457 participants, 2457 eyes) with neovascular AMD (Sarwar S, et al.; Cochrane Review 2016). The meta-analysis evaluated VIEW 1 and VIEW 2 trials (N=2457 participants, 2457 eyes) comparing aflibercept with ranibizumab in patients with subfoveal neovascular AMD who were treatment naive in the study eye. Both studies randomized patients to treatment with intravitreal injections of aflibercept 0.5 mg every 4 weeks, aflibercept 2 mg every 4 weeks, aflibercept 2 mg every 8 weeks after 3 initial monthly injections, or ranibizumab 0.5 mg every 4 weeks for a primary treatment period of 52 weeks. During a follow-up phase from weeks 52 to 96, all regimens were switched from the fixed monthly or bimonthly regimen to an as-needed regimen with a minimum quarterly dose. Changes in visual acuity, both gains and losses, were similar among aflibercept- and ranibizumab-treated eyes. Overall improvement in visual acuity correlated with anatomic improvements (e.g., retinal thickening, choroidal neovascularization [CNV] size) for both agents. At one year, participants in the aflibercept groups showed mean change in best-corrected visual acuity (BCVA) from baseline similar to that of participants in the ranibizumab groups. At two years, the mean change in BCVA from baseline was 7.2 ETDRS letters for aflibercept groups versus 7.9 for ranibizumab groups. At one year, the proportion of eyes that achieved dry retina was similar between aflibercept and ranibizumab groups. The authors concluded that current available information on adverse effects of each medication suggests that the safety profile of aflibercept is comparable with that of ranibizumab. Overall, occurrence of serious systemic adverse events was similar and comparable in aflibercept- and ranibizumab-treated groups at one year. 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. Sarwar et al. noted that no clinical trial that compared aflibercept versus bevacizumab for the treatment of individuals with neovascular AMD; however, several studies have compared ranibizumab versus bevacizumab for outcomes of neovascular AMD (Solomon 2016).

Several RCTs have compared the effects of the frequently used anti-VEGF agents, ranibizumab (Lucentis) and bevacizumab (Avastin), for the treatment of wet AMD since bevacizumab has not been FDA approved for intraocular injection and has been more cost-effective than ranibizumab.

Solomon et al. conducted a systematic review of the most frequently used intravitreal anti-VEGF agents to treat neovascular (wet) AMD, bevacizumab and ranibizumab. The review included only RCTs in which the 2 anti-VEGF agents had been compared directly. The authors located 6 RCTs (with 2806 participants) and compared the effect of intravitreal injections of bevacizumab relative to ranibizumab with respect to several different outcomes that are important to patients with wet AMD and their ophthalmologists. The study found no important difference between the 2 anti-VEFG agents for clinical outcomes such as BCVA, visual function, and lesion morphology through 2 years of follow-up. There is also no important difference in the most serious ocular complications; however, rates of serious ocular adverse events were small, that is, no more than 1%.

Overall efficacy results, in terms of visual acuity, appear similar for the drugs that have been compared. For example, efficacy between bevacizumab and ranibizumab was comparable in the Comparison of AMD Treatment Trials (CATT) and the Inhibition of VEGF in Age-related Choroidal Neovascularization trial (IVAN study). Aflibercept and ranibizumab were comparable for maintaining vision (loss of <15 letters) in the VIEW 1 and VIEW 2 trials. Most recently, brolucizumab was noninferior to aflibercept in the HAWK and HARRIER trials. Head-to-head trials have not compared bevacizumab versus aflibercept, or brolucizumab versus bevacizumab or ranibizumab. There may be differences among anti-VEGF agents in terms of resolution of fluid on OCT and durability of anti-VEGF effect in an individual patient. While it is not clear what produces individual variations in response to anti-VEGF agents, hypotheses such as anti-VEGF resistance and tachyphylaxis have been explored.

Bevacizumab and ranibizumab had equivalent effects on visual acuity when administered on the same dosing regimen.

- 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. **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.**

- IVAN study (2012, 2013) 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)

American Academy of Ophthalmology (AAO)

Age-Related Macular Degeneration Preferred Practice Patterns (PPO) (2019)
The AAO (2019) noted that treatments for neovascular AMD include intravitreal injection of anti-VEGF agents, photodynamic therapy, and use of antioxidant vitamins and zinc supplementation for slowing disease progression. Anti-VEGF agents (aflibercept, bevacizumab [off-label use], pegaptanib, and ranibizumab) are considered first-line treatment and most effective way to manage neovascular AMD. The guidelines did not recommend Macugen (pegaptanib) stating that unlike the other anti-VEGF agents that are currently available (ranibizumab, aflibercept, and bevacizumab), pegaptanib treatment does not improve visual acuity on average in patients with new-onset neovascular AMD and is rarely used in current clinical practice.

Diabetic Retinopathy PPP (2019)
According to the guidelines, treatment with laser, anti-VEGF agents, or intravitreal corticosteroids is cost-effective for managing DR to varying degrees. Intravitreal anti-VEGF agents are effective in the treatment of center-involved DME with vision loss. Laser photocoagulation surgery remains the preferred treatment for non-center-involved DME and pan-retinal photocoagulation surgery remains the mainstay treatment for proliferative. The PPP notes that the most serious complication of anti-VEGF injections is infectious endophthalmitis with rates between 0.019% and 0.09% in clinical trial settings and other complications, such as retinal detachment, cataract formation, and sustained elevated IOP are rare.

Retinal Vein Occlusions PPP (2019)
The AAO (2019) notes that macular edema may complicate both CRVOs and BRVOs and the first-line of treatment for associated macular edema is anti-VEGFs. Intravitreal corticosteroids, with the associated risk of glaucoma and cataract formation, have demonstrated efficacy. Also, laser photocoagulation surgery in BRVO has a potential role in treatment.

DEFINITIONS

Anti-Platelet Trialists' Collaboration (APTC): Defined arterial thromboembolic events (nonfatal myocardial infarction, nonfatal stroke, and vascular death), and death from all causes.

Intravitreal implant: A drug delivery system, injected or surgically implanted in the vitreous of the eye, for sustained release of a pharmacologic agent to the posterior and intermediate segments of the eye.

Neovascularization: The formation of abnormal new blood vessels

Retinopathy: Damage to the retina

Vascular endothelial growth factor (VEGF): VEGF plays an important role in both physiologic and pathologic angiogenesis and contributes to increased permeability across both the blood-retinal and blood-brain barriers. VEGF is a protein that stimulates the growth, proliferation, and survival of vascular endothelial cells. VEGF, through its promotion of angiogenesis and vascular permeability, is a central component of the pathologic process driving wet AMD, as well as other choroidal and retinal vascular disorders.

CODING INFORMATION

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. coverage is determined by the benefit document. this list of codes may not be all inclusive.

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

KEO June 3, 2021

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Policy History	Approval
Policy Developed Peer Review: Diana Cokingtin, MD	MCPC 9/17/2014
Revision IRO Peer Review. 9/20/2016. Practicing Physician. Board certified in Board certified in Ophthalmology, Surgery Vitreoretina (CA)	MCPC 12/14/2016
Revision IRO Peer Review. 7/1/2019. Practicing Physician. Board certified in Ophthalmology (CA) Notable revisions: Diabetic Retinopathy indication and applicable criterion and content added.	P&T Q3 2019
Annual Review No coverage criteria changes with this annual review. Minor revisions, including clarification and addition of language, however no change to intent. Notable update: Added newly approved pre-filled syringe dosage form.	P&T Q3 2020
IRO Peer Review. 5/12/2021. Practicing Physician. Board certified in Ophthalmology (CA) Notable revisions include: Added the following criteria: • To the 'Coverage Criteria for Initial Authorization' section in #6 'Labs/Reports/Documentation required' for congruency with the 'Reauthorization/Continuation of Treatment' criteria: 'Prescriber to maintain record of administration of intravitreal therapy (recorded in the procedure or post-procedure note following the completion of treatments) with the following information: name of the medication, dose/amount of drug administered, and treated eye (Right eye, Left eye, or Both eyes). Submit with re-authorization requests.' • To 'Reauthorization/Continuation of Treatment' section, #2 Response to treatment: 'Supportive findings from optical coherence tomography or fluorescein angiography' • To the 'Authorization Limit' section to address dosage increase: 'Members with an insufficient response during initial therapy administered every 4 weeks may continue with dosing every 4 weeks. Members with an inadequate response to maintenance therapy administered every 8 weeks may increase the dosing frequency up to every 4 weeks.' Removed the following criteria: • From the 'Continuation of Treatment' section under the 'Labs/Reports/Documentation required' ▪ 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	6/9/2021

**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.*