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Medication Policy Manual

Policy No: dru621

Topic: Intravitreal Vascular Endothelial Growth Factor (VEGF) Inhibitors:

- Beovu (brolucizumab)
- Eylea, Eylea HD (aflibercept); biosimilars: Ahzantive (aflibercept-mrbb), Enzeevu (aflibercept-abzv), Eydenzelt (aflibercept-boav), Opuviz (aflibercept-yszy), Pavblu (aflibercept-ayyh), Yesafili (aflibercept-jbvf)
- Lucentis (ranibizumab); biosimilars Byooviz, Cimerli (ranibizumab-eqrn), Nufymco (ranibizumab-leyk), Ranibizumab-nuna (unbranded), Ranluspec (ranibizumab-hkdz), Susvimo
- Vabysmo (faricimab-svoa)

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

The medications in this policy are all inhibitors of vascular endothelial growth factor (VEGF), which prevent the formation of new blood vessels. They are injected directly into the eye (intravitreal) to treat a variety of eye conditions, by reducing swelling (blood vessel leakage and inflammation). Susvimo is a newer formulation that delivers ranibizumab injection via ocular implant.

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Policy/Criteria

Most contracts require pre-authorization approval of intravitreal vascular endothelial growth factor (VEGF) inhibitors (as listed in *Table 1*) prior to coverage.

I. Continuation of therapy (COT): Intravitreal vascular endothelial growth factor (VEGF) inhibitors may be considered medically necessary for COT when criterion A or B below is met.

A. Both of the following (1 and 2):

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. **For Susvimo only**: Treatment with a lower-cost ranibizumab, including Byooviz (ranibizumab-nuna), Cimerli (ranibizumab-eqrn), Lucentis (ranibizumab), Nufymco (ranibizumab-leyk), Ranibizumab-nuna (unbranded), or Ranluspec (ranibizumab-hkdz) was ineffective, not tolerated, or use is contraindicated.

OR

B. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Intravitreal VEGF inhibitors may be considered medically necessary when there is clinical documentation that step therapy requirements below are met:

A. Step therapy requirements are considered met when:

1. Treatment with the required product(s) (as listed in *Table 1*) was ineffective, not tolerated, or use is contraindicated.

OR

2. There is evidence in the patient's paid medical claim history that the patient has used the required product(s) (as listed in *Table 1*).

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Table 1. Intravitreal VEGF Inhibitor Products

Product Group	Products	Step Therapy Requirements
Level 1	- bevacizumab	No PA required when used in the eye
Level 2	- Byooviz (ranibizumab-nuna) - Cimerli (ranibizumab-eqrn) - Lucentis (ranibizumab) - Nufymco (ranibizumab-leyk) - Ranibizumab-nuna (unbranded) - Ranluspec (ranibizumab-hkdz)	**1.** Treatment with a Level 1 product
Level 3	- Ahzantive (aflibercept-mrbb) - Beovu (brolucizumab-dbll) - Enzeevu (aflibercept-abzv) - Eydenzelt (aflibercept-boav) - Eylea (aflibercept) - Eylea HD (aflibercept) - Opuviz (aflibercept-yszy) - Pavblu (aflibercept-ayyh) - Yesafili (aflibercept-jbvf)	**1.** Treatment with a Level 1 product **AND** **2.** Treatment with a Level 2 product
Level 4	- Susvimo (ranibizumab injection via ocular implant) - Vabysmo (faricimab-svoa)	**1.** Treatment with a Level 1 product **AND** **2.** Treatment with a Level 2 product **AND** **3.** Treatment with a Level 3 product

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers intravitreal VEGF inhibitors coverable only under the medical benefit (as provider-administered medications).

B. Authorization **may** be reviewed annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

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Position Statement

- The intent of this policy is to cover higher cost branded VEGF inhibitors when lower cost options (as listed in the coverage criteria) are ineffective or not a treatment option, as detailed in the coverage criteria.
- Bevacizumab is the lowest cost VEGF inhibitor for the treatment of ocular conditions and therefore does not require pre-authorization (PA) for ocular conditions.
- Although intravitreal VEGF inhibitors have different indications, they have demonstrated evidence of efficacy for maintaining or improving visual acuity across various retinal disorders in clinical trials.
- Intravitreal VEGF inhibitors all work using the same mechanism of action by binding to the receptor binding site of active forms of VEGF-A. Likely because of similarities in mechanism of action, studies have not been able to demonstrate that one product is significantly superior to another in efficacy or safety (as detailed in the *Clinical Efficacy* sections below, by diagnosis).
    * Recently approved Vabysmo (faricimab-svoa) works by inhibiting both VEGF-A and angiopoietin-2 (Ang-2). However, per the FDA labeling, the contribution of Ang-2 inhibition to treatment effect remains unknown at this time. [1]
    * Susvimo (ranibizumab injection via ocular implant) is a long-acting formulation of ranibizumab. Susvimo consists of a small surgically implanted "port" that releases ranibizumab continually for up to six months, at which time the port is refilled. In clinical trials, Susvimo (ranibizumab injection via ocular implant) was non-inferior to Lucentis (ranibizumab intravitreal injection). However, there was a temporary drop in visual acuity and increase in ocular adverse events with Susvimo (ranibizumab injection via ocular implant).
- Byooviz (ranibizumab-nuna), Cimerli (ranibizumab-eqrn), Nufymco (ranibizumab-leyk), Ranluspec (ranibizumab-hkdz), and Ranibizumab-nuna (unbranded) are FDA-approved biosimilars to Lucentis (ranibizumab). These biosimilars offer equally effective alternatives to the reference product, Lucentis (ranibizumab intravitreal injection), as well as lower cost than Susvimo (ranibizumab injection via ocular implant). FDA-approved biosimilar medications are clinically not meaningfully different than their reference products (i.e., therapeutically equivalent). Although small differences in clinically inactive portions of the molecule may exist, the FDA approval certifies that the manufacturer has shown their product to be identical in function. There is no scientific basis to clinically prefer one FDA-approved product over another; given similar efficacy and safety, most contracts consider more costly products not medically necessary.
- Evidence-based recommendations and clinical guidelines do not differentiate the VEGF inhibitors in clinical practice recommendations. Evidence-based recommendations and clinical guidelines equally recommend the use of VEGF inhibitors, including bevacizumab, for the treatment of neovascular (wet) age-related macular degeneration (wAMD), macular edema secondary to retinal vein occlusion (RVO), retinopathy of prematurity (ROP), and diabetic macular edema (DME; including diabetic retinopathy associated with DME).

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- Despite the availability of well-designed studies that have shown similar efficacy between VEGF inhibitors, there is an absence of studies and evidence-based guidelines to guide treatment in refractory AMD individuals who have failed one or more VEGF inhibitors, due to lack of or incomplete response. Defining non-responders to treatment is an additional challenge among clinicians given that there is no universally accepted nomenclature for describing different types of non-responsiveness. Multiple clinical features are used in practice as measures of treatment efficacy and response (improvement in visual acuity, reduction in intraretinal or subretinal fluid, increase in central macular thickness etc.); patients without a particular response may or may not be deemed as non-responders depending on provider approach.
- In clinical practice, approaches to subsequent treatment for refractory AMD individuals include reducing treatment intervals, increasing the dose of the current treatment if available, or switching to a different medication.
- Higher-cost VEGF products, including Eylea / Eylea HD (aflibercept) have been studied in other vascular-related ocular conditions. The clinical benefit of higher-cost VEGF products in these indications is uncertain to date.
- Previous concerns over the use of compounded or repackaged products, such as bevacizumab, have been alleviated by the FDA's 2013 Drug Quality and Security Act, which provides better oversight of compounding pharmacies. In addition, the American Society of Retina Specialists has published online safety information about compounding pharmacies to help retina specialists choose high-quality providers of bevacizumab. Furthermore, in February 2015 the FDA issued Draft Guidance regarding drug compounding and repackaging of biologics to further standardize quality of bevacizumab. [2-4]

Clinical Efficacy

Neovascular (wet) Age-Related Macular Degeneration (AMD)

- Intravitreal VEGF inhibitors have similar effectiveness for wet AMD. They all have been shown to maintain or improve vision based clinical trials. Systematic reviews have concluded that the comparators have similar efficacy.
    * One high-quality systematic review of Avastin (bevacizumab) in the treatment of wAMD concluded that it improves visual acuity and central retinal thickness (moderate correlate to visual acuity) and is more effective than photodynamic therapy (without verteporfin). [5]
    * A 2019 systematic review of VEGF inhibitors in wAMD concluded that there were no major differences with respect to vision related outcomes comparing Lucentis (ranibizumab) and Avastin (bevacizumab) after one year of treatment. Of note, the review did not include any trials with Eylea (aflibercept) or Beovu (brolucizumab-dbll). [6]
    * A 2016 systematic review focusing on Eylea (aflibercept) concluded that intravitreal aflibercept has similar efficacy to Lucentis (ranibizumab) in terms of improvement and stability in visual acuity after one and two years of treatment. [7]

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    * Beovu (brolucizumab-dbll) was evaluated in two phase 3 randomized, controlled trials: HAWK and HARRIER. Both studies had nearly identical designs and endpoints. Results demonstrated the brolucizumab was non-inferior to aflibercept for maintaining visual acuity. [8]
    * CATT1 was a multicenter, single-blind, noninferiority trial where 1,208 patients with neovascular AMD were assigned to receive Lucentis or Avastin each month or on an as needed basis after each monthly evaluation. Primary outcome was defined as the mean visual acuity change after 1 year and noninferiority limit of 5 letters on the eye chart. Monthly administrations of Avastin or Lucentis had similar efficacy, with 8.0 and 8.5 letters gained, respectively. Avastin and Lucentis administered as needed were also equivalent to each other, with 5.9 and 6.8 letters gained, respectively. Both drugs dramatically reduced retinal and subretinal fluid, but Lucentis eliminated fluid more often. At 1 year, Avastin and Lucentis had equivalent effects on visual acuity when administered according to the same schedule. The proportion of patients with no fluid on OCT after 1 year were 19.2% in those receiving Avastin as needed and 43.7% for those receiving Lucentis as needed.[9]

- The American Academy of Ophthalmology (AAO) guidelines state that in patients with wAMD, intravitreal injection therapy using VEGF inhibitors are the most effective way to manage wAMD and represents the first line of treatment. Guidelines include Eylea (aflibercept), Avastin (bevacizumab), Lucentis (ranibizumab), and Beovu (brolucizumab-dbll) for the treatment of wet AMD. The guidelines were updated in 2024 to include Vabysmo (faricimab-svoa) and Susvimo (ranibizumab implant), along with biosimilars of ranibizumab and aflibercept. An article from the AAO mentions that patients may differ in how their eyes respond to one treatment versus another. Therefore, switching to another therapy may be needed to improve response. [10]

Diabetic Macular Edema (DME)

- There is moderate certainty that VEGF inhibitors improve visual acuity in patients with DME; however, there is insufficient evidence to demonstrate that one VEGF inhibitor is clinically superior to another in the treatment of DME based on one high-quality systematic review and one government-sponsored comparative study.
    * A Cochrane systematic review (2018) concluded that Eylea (aflibercept), Avastin (bevacizumab), and Lucentis (ranibizumab) are more effective than laser photocoagulation in improving visual acuity (i.e., likelihood of gaining three or more lines of vision). Although there were no significant sub-group differences in visual acuity between the VEGF inhibitors, there was insufficient power to detect a difference between them. [11]
    * A government-sponsored trial (PROTOCOL T) evaluated mean improvement in visual acuity for up to two years in patients with DME treated in a randomized fashion 1:1:1, with Eylea (aflibercept) 2mg, Avastin (bevacizumab) 1.25mg or Lucentis (ranibizumab) 0.3mg, every 4 weeks: [12 13]
        - The trial concluded that there was no clinically meaningful difference in improvement in visual acuity in the overall DME population.

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    - It was noted that Eylea (aflibercept) was modestly more effective (approximate mean improvement of 6 letters) at improving visual acuity relative to the other VEGF inhibitors in a subset of patients with lower baseline visual acuity at the 1- and 2-year follow-up; however, there was low confidence in the trial results due to an imbalance in concomitant treatment between study arms, potential for bias as investigators were not blinded to treatment, and that results may not apply to eyes with persistent or recurrent DME that are already being treated with anti-VEGF inhibitors, based on study eligibility criteria.

- More recently, a new formulation of Susvimo (ranibizumab) was approved for delivery of ranibizumab injection via an implanted port. Clinical trials of Susvimo (ranibizumab via ocular implant) demonstrated comparable efficacy results to Lucentis (ranibizumab intravitreal injections); however, the implant was associated with a higher incidence of adverse events, including a 3-fold higher rate of endophthalmitis. The clinical efficacy and safety of Susvimo (ranibizumab via ocular implant) was assessed in one randomized, visual assessor-masked, non-inferiority trial (Archway; n=415). [14]
    * Patients diagnosed with wAMD within the nine months prior to screening and received at least three doses of intravitreal VEGF inhibitors. Only VEGF responders were included in the trial.
    * Patients were randomized to Susvimo (ranibizumab via ocular implant) with refills every 24 weeks or Lucentis (ranibizumab intravitreal injections) every 4 weeks.
    * The primary efficacy endpoint was the change from baseline in best-corrected visual acuity (BCVA) score averaged over week 36 and 40.
    * Efficacy of Susvimo (ranibizumab via ocular implant) was noninferior to Lucentis (ranibizumab intravitreal injections) with a change from baseline BCVA of +0.2 and +0.5, respectively at 36-40 weeks [difference of -0.3 (CI -1.7 to 1.1) meeting non-inferiority].
    * However, the trial was relatively short, given the chronic progressive nature of wAMD. Therefore, the durability of the treatment effect is unknown.
    * Of note, patients treated with the Susvimo (ranibizumab via ocular implant) experienced a transient and reversible postsurgical drop in visual acuity, as measured by Early Treatment Diabetic Retinopathy Study Letters (ETDRS), after implant insertion, with vision returning to baseline by week 8.
    * In addition, safety concerns inherent to an ocular implant may limit the utility of Susvimo (ranibizumab via ocular implant) (see *Safety* section below for additional details).
- The American Academy of Ophthalmology guidelines support the use of VEGF inhibitors, including Lucentis (ranibizumab), Eylea (aflibercept), and Avastin (bevacizumab) in the treatment of DME (including diabetic retinopathy associated with DME). [15 16]
    * AAO recommendations were based on trials comparing Eylea (aflibercept), Avastin (bevacizumab), and Lucentis (ranibizumab) to focal laser treatment

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(READ-2, BOLT, AND DA VINCI studies, respectively). All trials showed that treatment with VEGF inhibitors resulted in statistically and clinically significant improvements in visual acuity in patients with DME after one to two years of treatment compared to laser treatment.

* In the BOLT study, Avastin (bevacizumab) was also shown to reduce the level of severity of diabetic retinopathy in patients with DME over the 12-month treatment period whereas the severity remained relatively stable in patients who received laser therapy. [17]

* The guidelines were updated in 2024 to include of newer VEGF products, such as Susvimo (ranibizumab injection via ocular implant), Vabysmo (faricimab-svoa), and the biosimilars of ranibizumab and aflibercept.

Diabetic Retinopathy (without DME)

- Treatment with Lucentis (ranibizumab) demonstrated efficacy in the treatment of diabetic retinopathy without diabetic macular edema in the NIH-funded Diabetic Retinopathy Clinical Research Network Study. [18 19] The study compared Lucentis (ranibizumab) to panretinal laser therapy in patients with diabetic retinopathy, and found that patients both with and without diabetic macular edema had improved short-term and 2-year outcomes with Lucentis (ranibizumab) compared to panretinal or scatter photocoagulation laser therapy. [18]
- The American Academy of Ophthalmology guidelines support the use of VEGF inhibitors, including Lucentis (ranibizumab), Eylea (aflibercept), and Avastin (bevacizumab) in the treatment of DME (including diabetic retinopathy associated with DME). [15 16] [See *Diabetic Macular Edema* above, for details]
- Trials are ongoing for the use of Beovu (brolucizumab-dbll) in diabetic retinopathy. [20]

Retinal Vein Occlusion

- There is moderate certainty that VEGF inhibitors [Eylea (aflibercept), Avastin (bevacizumab), and Lucentis (ranibizumab)] are more effective than sham injection or laser therapy in maintaining or improving visual acuity in patients with macular edema secondary to RVO (branch and central; BRVO, CRVO) based on two Cochrane systematic reviews (2020); however, there is insufficient evidence to demonstrate that one VEGF inhibitor is clinically superior to another due to the lack of direct comparative evidence. [21 22]
- More recently, one non-inferiority LEAVO trial evaluated Lucentis (ranibizumab), Eylea (aflibercept), or bevacizumab in patients with CRVO (n = 463). [23] The pre-defined null hypothesis that Eylea (aflibercept) and bevacizumab are each inferior to Lucentis (ranibizumab), tested with a non-inferiority margin of –5 visual acuity letters over 100 weeks. The study demonstrated that Eylea (aflibercept) was non-inferior to Lucentis (ranibizumab), but not superior. However, the study was unable to demonstrate non-inferiority of bevacizumab to Lucentis (ranibizumab). Therefore, the aforementioned conclusion remains unchanged: there is insufficient evidence to demonstrate that one VEGF inhibitor is clinically superior to another due to the lack of direct comparative evidence.

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- Results from two randomized, multicenter, phase III trials (BALATON and COMINO) demonstrated monthly treatment with Vabysmo (faricimab-svoa) provided early and sustained improvement in vision in individuals with branch and central RVO, meeting the primary endpoint of non-inferior visual acuity gains at 24 weeks, compared to Eylea (aflibercept). The BCVA gains from baseline at week 24 with Vabysmo (faricimab-svoa) were noninferior to Eylea (aflibercept) in BALATON (adjusted mean [95% confidence interval] change: +16.9 letters [15.7, 18.1] vs. +17.5 letters [16.3, 18.6]) and COMINO (+16.9 letters [15.4, 18.3] vs. +17.3 letters [15.9, 18.8]). [24]
- Evidence-based recommendations from UpToDate, the American Academy of Ophthalmology, and the Centers for Medicare and Medicaid Services support the use of VEGF inhibitors [Eylea (aflibercept), Avastin (bevacizumab), Lucentis (ranibizumab), and Vabysmo (faricimab-svoa)] for the treatment of macular edema secondary to retinal vein occlusion. [25-27] The American Academy of Ophthalmology guidelines were updated in 2026 to include ranibizumab biosimilars. As of the publication of this policy, implanted ranibizumab via ocular implant (Susvimo) does not have an approved indication for retinal vein occlusion.

Myopic Choroidal Neovascularization (mCNV)

- A Cochrane systematic review (2016) concluded that there is low-to-moderate certainty evidence for the efficacy of VEGF inhibitors to treat mCNV at one year and two years. [28] The authors also concluded that Lucentis (ranibizumab) and Avastin (bevacizumab) are equivalent in terms of efficacy in the treatment of patients with mCNV.
- Trials are ongoing for the use of Beovu (brolucizumab-dbll) in mCNV. [20]

Retinopathy of Prematurity (ROP)

- Retinopathy of prematurity (ROP) is a developmental vascular disorder that occurs in the retina of preterm infants and can lead to blindness. The incidence and severity of ROP increase with decreasing gestational age (GA) and birth weight. Severe ROP develops in approximately 40 percent of infants born at 22 to 25 weeks GA, 20 percent of those born at 25 to <27 weeks GA, and <5 percent of those born at 27 to 30 weeks GA. [42]
- Standard of care treatments for ROP include laser treatment and anti-VEGF injections including bevacizumab, ranibizumab, and aflibercept. [41]
- There is no evidence that any one anti-VEGF is safer or more effective than another for the treatment of ROP.

Refractory AMD

- Patients suffering from refractory or recurrent neovascular AMD (nAMD) may develop mechanisms of resistance to VEGF inhibitors which results in a diminished therapeutic effect. Most treatment approaches to refractory AMD are guided by provider clinical experience or preference, without specific guidelines available for this patient population.
- Evidence for treating refractory nAMD is limited to small, pilot studies or retrospective case reviews, not randomized controlled trials of significant size.
- The LAST study, a prospective pilot study of 9 subjects with subfoveal neovascular AMD with persistent subretinal or intraretinal fluid despite 6 months of treatment with either Lucentis (ranibizumab) 0.5mg/0.05ml or Avastin (bevacizumab) 1.25mg/0.05ml intravitreally, showed that at 6 months, high-dose Lucentis (ranibizumab) 2mg/0.05ml

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had the potential to maintain or improve visual acuity in patients with persistent fluid secondary to nAMD and despite prior monthly treatment with standard doses of VEGF-inhibitors. There was a mean improvement in visual acuity of 6 ETDRS letters; however, given the small sample size, it was not possible to make a statistical comparison between the two treatment groups. [29]

Other Uses

- The use of any VEGF inhibitor in conjunction with other VEGF inhibitors is considered investigational as there is no evidence evaluating the efficacy or safety of combination therapy.
- Trials of Eylea (aflibercept) in a variety of other conditions such as radiation retinopathy, central serous chorioretinopathy, and pathologic myopia are ongoing and are considered investigational due to lack of published, high-quality data.
- Published data evaluating Lucentis (ranibizumab) in several other conditions is preliminary. Larger well-controlled trials are needed to determine the clinical benefit of Lucentis (ranibizumab) in these conditions.
    * One study in 37 patients with retinal angiomatous proliferation evaluated Lucentis (ranibizumab) alone, and either Lucentis (ranibizumab) or intravitreal triamcinolone plus photodynamic therapy. Disease stabilization occurred in all three groups; however, a trend toward better visual acuity and anatomic restoration occurred in the triamcinolone/photodynamic therapy group. These results were confirmed at 3 years. [30 31]
    * A single-center pilot study in 10 patients with primary pterygia evaluated the tolerability of Lucentis (ranibizumab) either prior to surgery or at the time of surgery. [32]
    * A single-center pilot study in 10 patients undergoing trabeculectomy evaluated Lucentis (ranibizumab) to assist in wound healing when given with topical mitomycin C. [33]
    * Lucentis (ranibizumab) was evaluated versus photodynamic therapy in a single-center pilot study in 16 patients with chronic central serous chorioretinopathy. [34]

Safety [35]

- Intravitreal VEGF inhibitors have been associated with inflammation, blurred vision, corneal edema, eye discharge and irritation, and hypertension. However, a 2016 Cochrane review concluded that neither Eylea (aflibercept) or Lucentis (ranibizumab) drug produces a greater incidence of systemic or vision-threatening complications. [7]
- Updates to prescribing information for Eylea/Eylea HD (aflibercept) and Vabysmo (faricimab-svoa) include warnings/precautions for the potential of retinal vasculitis with or without occlusion and arterial thromboembolic events (ATEs) based on post-marketing experience.
- Additional serious adverse effects reported with intravitreal VEGF inhibitors include endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. After injection, patients should be advised to seek immediate care if the treated eye becomes red, painful, sensitive to light, or they notice a change in vision. There is no known difference between the safety profile of the currently available biosimilars and the innovator products.

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- Although Lucentis (ranibizumab) has sufficient clinical safety experience, experience with the implant formulation of Susvimo (ranibizumab) is limited. In clinical trials, Susvimo (ranibizumab injection via ocular implant) was associated with a higher incidence of adverse events compared to monthly intravitreal injections of Lucentis (ranibizumab), including a three-fold higher rate of endophthalmitis, for which a box warning is included in its prescribing information. In addition, the Susvimo (ranibizumab injection via ocular implant) and/or implant-related procedures have been associated with infection, hemorrhage, retinal detachment, implant dislocation, and decrease in visual acuity. [36]
- *Cardiovascular (CV) safety*: A meta-analysis evaluating the CV safety of intravitreal VEGF inhibitors in patients with wet AMD, DME, or RVO concluded that VEGF inhibitors, specifically Avastin (bevacizumab) and Lucentis (ranibizumab), are not associated with a significant increase in risk of systemic CV and hemorrhagic events or in overall mortality, stroke, or CV mortality in elderly patients. However, the studies and meta-analysis were not sufficiently powered to correctly assess these risks. [37]
- *Comparative safety*: The trial conducted by the CATT research group comparing Lucentis (ranibizumab) to Avastin (bevacizumab) for the treatment of wet AMD found the following regarding safety: [18 19]
    * A statistically significant difference was seen at 52 weeks in the rates of serious systemic adverse events between the Lucentis (ranibizumab) and Avastin (bevacizumab) groups (19.0% vs 24.1%, P = 0.04).
    * A significant difference was also seen at 2 years [39.9% Avastin (bevacizumab) vs 31.7% Lucentis (ranibizumab); adjusted risk ratio 1.30; 95% CI: 1.07, 1.57; P = 0.009].
    * This difference was largely due to hospitalizations for infections such as pneumonia and urinary tract infections. It is uncertain if these events were related to either medication.
- *Compounded VEGF inhibitors* - Avastin (bevacizumab) is listed in national treatment guidelines and is recognized by the Centers for Medicare and Medicaid Services as a safe and effective treatment option for wet AMD, DME, and RVO. [13]
    * Avastin (bevacizumab), when used in the eye, must be extemporaneously compounded to achieve the appropriate dose. In 2011, a group of cases of endophthalmitis were reported with the use of Avastin (bevacizumab) which was determined to be the result of unsafe practices by one compounding pharmacy. [7 38 39]
    * While the use of Avastin (bevacizumab) continues to be associated with the risk of endophthalmitis, all intravitreal injections, including commercially available preparations of Eylea (aflibercept), Macugen (pegaptanib), and Lucentis (ranibizumab) carry this risk. [40 41]

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Dosing [35]

- Eylea (aflibercept) 2 mg is injected intravitreally (into the eye) every 4 weeks for 12 weeks, then every 8 weeks. After one year of effective therapy patients may also be treated with one dose every 12 weeks. Eylea HD (aflibercept) 8 mg is injected intravitreally every 4 weeks (+/- 7 days) for the first three doses, followed by 8 mg every 8 to 16 weeks (+/- 1 week).
- Avastin (bevacizumab) 1.25 mg is injected intravitreally (into the eye) monthly or as needed.
- Beovu (brolucizumab) 6 mg is injected monthly for the first three doses, followed by 6 mg (one dose) every 8–12 weeks.
- Ranibizumab (biosimilars, Lucentis) 0.5 mg is injected intravitreally (into the eye) every 1 to 3 months.
- The Susvimo ocular implant system is initially inserted into the eye and the 2 mg ranibizumab injection solution refilled every 6 months.
- Vabysmo (faricimab-svoa) is injected monthly for the first four doses, followed by 6 mg (one dose) every 4-16 weeks, with significant variation in dosing dependent on indication and response to therapy.

Appendix 1: Nomenclature of ocular conditions treated with VEGF Inhibitors [25 42 43]

Diagnosis	Synonyms
Neovascular (wet) age-related macular degeneration	Exudative senile macular degeneration
	Age-related macular degeneration (ARMD)
	Choroidal neovascularization (CNV)
Diabetic Macular Edema and Diabetic Retinopathy	Diabetic macular edema (DME) associated with diabetic retinopathy
	DME due to Type 1 or Type 2 diabetic retinopathy
	DME due to nonproliferative or proliferative diabetic retinopathy (mild, moderate, or severe)
	Center involving diabetic macular edema
	Diabetic retinal edema
	Clinically significant diabetic macular edema (CSME)
Myopic choroidal neovascularization	Choroidal neovascularization secondary to pathologic myopia (mCNV)
	Pathologic myopia
Macular edema associated with Retinal Vein Occlusion	Macular edema associated with central retinal vein occlusion (CRVO)
	Macular edema associated with branch retinal vein occlusion (BRVO)
	Macular edema associated with tributary (branch) retinal vein occlusion

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Codes	Number	Description
HCPCS	Q5150	Injection, aflibercept-mrbb, biosimilar (Ahzantive), 1 mg
HCPCS	Q5126	Injection, bevacizumab-maly, biosimilar (Alymsys), 10 mg
HCPCS	J9035	Injection, bevacizumab, (Avastin) 10 mg
HCPCS	J0179	Injection, brolucizumab-dbll (Beovu), 1 mg
HCPCS	Q5124	Injection, ranibizumab-nuna, biosimilar, (Byooviz), 0.1 mg
HCPCS	Q5128	Injection, ranibizumab-eqrn (Cimerli), biosimilar, 0.1 mg
HCPCS	Q5149	Injection, aflibercept-abzv, biosimilar (Enzeevu), 1 mg
HCPCS	J0178	Injection, aflibercept (Eylea), 1 mg
HCPCS	J0177	Injection, aflibercept (Eylea HD), 8mg
HCPCS	J2778	Injection, ranibizumab (Lucentis), 0.1 mg
HCPCS	Q5107	Injection, bevacizumab-awwb, biosimilar, (Mvasi), 10 mg
HCPCS	Q5153	Injection, aflibercept-yszy, (Opuviz), 1 mg
HCPCS	Q5147	Injection, aflibercept-ayyh, biosimilar (Pavblu), 1 mg
HCPCS	J2779	Injection, ranibizumab, via intravitreal implant (Susvimo), 0.1 mg
HCPCS	J2777	Injection, faricimab-svoa (Vabysmo), 0.1 mg
HCPCS	Q5129	Injection, bevacizumab-adcd, biosimilar, (Vegzelma), 10 mg
HCPCS	Q5155	Injection, aflibercept-jbvf (Yesafili), biosimilar, 1 mg
HCPCS	Q5118	Injection, bevacizumab-bvzr, biosimilar, (Zirabev), 10 mg

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Revision History

Revision Date	Revision Summary
9/1/2026	• Readded biosimilar Cimerli (ranibizumab-eqrn) due to market reintroduction. • Added new biosimilar Ranluspec (ranibizumab-hkdz) to Level 2.
1/22/2026	• Added new biosimilar Eydenzelt (aflibercept-boav) to Level 3. • Added new biosimilars Nufymco (ranibizumab-leyk) and Ranibizumab-nuna (unbranded) to Level 2.
10/2/2025	• Added HCPCS codes for Ahzantive (aflibercept-mrbb), Enzeevu (aflibercept-abzv), Opuviz (aflibercept-yszy), Pavblu (aflibercept-ayyh), and Yesafili (aflibercept-jbvf). • Added information about neovascular (wet) age-related macular degeneration (nAMD) along with guideline updates to backend of policy.
4/3/2025	Removed Cimerli (ranibizumab-eqrn) from policy due to manufacturer discontinuation.
9/19/2024	• Added newly FDA-approved biosimilars Ahzantive (aflibercept-mrbb), Enzeevu (aflibercept-abzv) and Pavblu (aflibercept-ayyh) to Level 3. • Moved Lucentis (ranibizumab) from a Level 3 to Level 2 product. • Added HCPCS code for Cimerli (ranibizumab-eqrn).
6/20/2024	• Added newly FDA-approved biosimilars Opuviz (aflibercept-yszy) and Yesafili (aflibercept-jbvf) to policy. • HCPCS Appendix updated with new Eylea HD code (J0177).
3/21/2024	Removed 90-day lookback in criterion II.A.2 (certain agents have a 4-month dosing schedule or response to therapy may dictate an extended dosing schedule).
12/7/2023	Added Eylea HD, a new aflibercept higher dose product, to policy.
9/14/2023	No criteria changes with this annual review. Added information about retinopathy of prematurity (ROP) to backend of policy.
3/16/2023	No changes to criteria with this annual update.
9/23/2022	• Updated format of step therapy requirements for operational clarity. No change to intent. • Added Cimerli (ranibizumab-eqrn) to policy as a Level 2 product.
3/18/2022	• Updated step therapy with lower-cost VEGFs (bevacizumab, biosimilars) to a claim look-back, for operational consistency. • Added step therapy with Lucentis (ranibizumab) to the ranibizumab injection via ocular implant (Susvimo) criteria. • Clarified name of formulation: ranibizumab injection via ocular implant (Susvimo). • Added Vabysmo (faricimab-svoa) per charter.

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Revision Date	Revision Summary
10/15/2021	Effective 1/1/2022: • Added newly FDA-approved biosimilar Byooviz (ranibizumab-nuna) to policy. • Updated step therapy criteria to require use of Byooviz (ranibizumab-nuna) prior to coverage of Eylea (aflibercept), Beovu (brolucizumab), or Lucentis (ranibizumab) in addition to bevacizumab. • Added Susvimo (ranibizumab) per charter.
4/21/2021	COT language added; no other changes to criteria with this annual update.
4/22/2020	No changes to criteria with this annual update.
1/22/2020	• New policy (effective 2/15/2020. Replaces individual drug coverage policies for Lucentis (ranibizumab) and Eylea (aflibercept). • Coverage criteria for Beovu (brolucizumab) have been added. • Limits use to those patients in which bevacizumab has been ineffective when used in the eye, unless contraindicated.

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