Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCBIO015.0225	**BIOLOGICAL** **OPHTHALMIC VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) INHIBITORS** See Table 4 for medications covered by policy
Effective Date: 4/1/2025	**Review/Revised Date**: 01/18, 05/18, 10/18, 10/19, 10/20, 11/20, 04/21, 07/21, 04/22, 08/22, 11/22, 05/23, 04/24, 05/24, 02/25 (JEF)
Original Effective Date: 05/18	**P&T Committee Meeting Date**: 02/18, 12/18, 08/19, 12/19, 10/20 (off-cycle), 12/20, 06/21, 08/21, 06/22, 07/22, 08/22, 12/22, 06/23, 04/24, 06/24, 02/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For **initiation of therapy** with the requested medication (new start): Must have one of the following diagnoses and meet any required criteria:
    a. **Neovascular (wet) age-related macular degeneration (AMD):**
        i. For faricimab (Vabysmo®) and brolucizumab (Beovu®), and Eylea® HD: Documentation that ALL the following agents have been ineffective, not tolerated, or contraindicated or rationale is provided why therapy is not appropriate for the patient:
            1) bevacizumab
            2) aflibercept (Eylea®) or aflibercept-ayyh (Pavblu®)
            3) ranibizumab (Lucentis®), ranibizumab-nuna (Byooviz®), or ranibizumab-eqrn (Cimerli®)
        ii. For ranibizumab implant (Susvimo®):
            1) Documentation that bevacizumab and aflibercept (Eylea®)/ aflibercept-ayyh (Pavblu®) have been ineffective, not tolerated, or contraindicated or rationale is provided why therapy is not appropriate for the patient AND
            2) Documentation of previous response to at least two intravitreal injections of ranibizumab (Lucentis®),

ranibizumab-eqrn (Cimerli®), or ranibizumab-nuna (Byooviz®) AND

3) Documentation that increased risk of endophthalmitis associated with ranibizumab (Susvimo®) has been discussed with the patient

b. **Diabetic macular edema or Diabetic retinopathy:**
   i. For faricimab (Vabysmo®), brolucizumab (Beovu®), and Eylea® HD: Documentation that ALL the following agents have been ineffective, not tolerated, or contraindicated or rationale is provided why therapy is not appropriate for the patient:
      1) bevacizumab
      2) aflibercept (Eylea®) or aflibercept-ayyh (Pavblu®)
      3) ranibizumab (Lucentis®), ranibizumab-nuna (Byooviz®), or ranibizumab-eqrn (Cimerli®)

c. **Macular edema following retinal vein occlusion:**
   i. For faricimab (Vabysmo®) and Eylea® HD: Documentation that ALL the following agents have been ineffective, not tolerated, or contraindicated or rationale is provided why therapy is not appropriate for the patient:
      1) bevacizumab
      2) aflibercept (Eylea®) or aflibercept-ayyh (Pavblu®)
      3) ranibizumab (Lucentis®), ranibizumab-nuna (Byooviz®), or ranibizumab-eqrn (Cimerli®)

2. For **patients established on therapy** with the requested agent (within the previous year): Documentation of positive response to therapy (such as stabilization or improvement in vision)

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed and administered by an ophthalmologist or retinal specialist

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

QUANTITY LIMITS:

Approval may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines and are subject to medical claims audits. (See Table 1 for dosing guidelines)

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Brolucizumab (Beovu®), ranibizumab (Lucentis®), ranibizumab-eqrn (Cimerli®), aflibercept injection (Eylea®), aflibercept-ayyh (Pavblu®), higher dose aflibercept injection (Eylea® HD), ranibizumab-nuna (Byooviz®), ranibizumab (Susvimo®), and faricimab (Vabysmo®) are vascular endothelial growth factor (VEGF) inhibitors used for the treatment of a variety of ophthalmic conditions. These products are administered by intravitreal injection. Ranibizumab (Susvimo®) is an intravitreal injection that is injected via the Susvimo® ocular implant.

FDA APPROVED INDICATIONS:

Brolucizumab (Beovu®)

- Neovascular (Wet) Age-related Macular Degeneration (AMD)
- Diabetic Macular Edema (DME)

Ranibizumab (Lucentis®) and Ranibizumab-eqrn (Cimerli®)

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)
- Myopic Choroidal Neovascularization (mCNV)

Aflibercept (Eylea®)

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)

- Diabetic Retinopathy (DR)
- Retinopathy of Prematurity (ROP)

Aflibercept-ayyh (Pavblu®)

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)

Higher dose aflibercept (Eylea® HD)

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)

Ranibizumab – nuna (Byooviz®)

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Myopic Choroidal Neovascularization (mCNV)

Ranibizumab (Susvimo®)

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

Faricimab (Vabysmo®)

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Diabetic Macular Edema (DME)
- Macular Edema Following Retinal Vein Occlusion (RVO)

POSITION STATEMENT:

- Age-related macular degeneration (AMD), diabetic retinopathy (DR), and diabetic macular edema (DME) are leading causes of blindness and severe visual impairment. Intravitreal injection of a VEGF inhibitor is an effective therapy and first line treatment for these conditions. VEGF inhibitors work to improve visual acuity by reducing leakage from blood vessels, preventing proliferation of new abnormal vessels and decreasing swelling of the retina.
- Ranibizumab is a recombinant monoclonal antibody, ophthalmic VEGF Inhibitor. Ranibizumab has been approved by the FDA for the treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR) and Myopic Choroidal Neovascularization (mCNV).
- Aflibercept is a fully human recombinant fusion protein that inhibits VEGF. It is approved by FDA for AMD, RVO and DME.
- Pegaptanib is an aptamer, a pegylated modified oligonucleotide, which is a selective VEGF antagonist. It is FDA approved only for the treatment of AMD. Of note, pegaptanib (Macugen®) has discontinued marketing status per the FDA.

- Brolucizumab recombinant human vascular endothelial growth factor inhibitor. Brolucizumab-dbll is a humanized monoclonal single-chain Fv (scFv) antibody fragment
- Bevacizumab is the full-length monoclonal antibody from which ranibizumab is derived. It is FDA approved for intravenous treatment of various malignancies. However, it is also used off-label for AMD, DME, RVO and DR. While bevacizumab use is off-label it 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.
- Aflibercept, bevacizumab, pegaptanib and ranibizumab all work using the same mechanism of action; by binding to the receptor binding site of active forms of VEGF-A.
- Brolucizumab was compared to aflibercept in the HAWK and HARRIER trials for the treatment of wet AMD. Brolucizumab was non-inferior to aflibercept in mean best-corrected visual acuity (BCVA) change from baseline to Week 48. Brolucizumab showed greater reduction in central subfield thickness (CST), and fewer patients had intra-retinal (IRF) and/or sub-retinal fluid (SRF) compared to the aflibercept treated patient. Brolucizumab was also compared to aflibercept in the KESTREL and KITE trials for the treatment of DME. In both studies, BEOVU was non-inferior to aflibercept for the change in BCVA from baseline to Week 52.
- For treatment of wet AMD, there have been two controlled trials which found that aflibercept was similar to bevacizumab in effectiveness. The NIH-sponsored Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration CATT study suggest that there were no major differences with respect to vision related outcomes between the therapies after one year of treatment. The American Academy of Ophthalmology (AAO) guidelines recommend aflibercept, bevacizumab or ranibizumab for the treatment of wet AMD. The AAO does not recommend the use of pegaptanib in the treatment of as the other therapies have been shown to provide greater benefit with less toxicity.
- For treatment of DME there was a large 1-year study sponsored by the NIH that randomized 660 adults with diabetic macular edema to intravitreal aflibercept 2 mg, bevacizumab 1.25 mg, or ranibizumab 0.3 mg every four weeks. In patients with mild initial visual acuity loss (visual acuity letter score 69-78), there were no significant differences in mean visual acuity at one year between the three groups. In patients with a visual acuity letter score <69, the mean improvement was significantly better with aflibercept (18.9 letters) than with ranibizumab (14.2) or bevacizumab (11.8). The American Academy of Ophthalmology guidelines support the use of aflibercept, bevacizumab or ranibizumab in the treatment of DME.

- Safety: There is low certainty in the evidence demonstrating differences in adverse events between intravitreal VEGF inhibitors. Bevacizumab must be compounded and repackaged and therefore there may be safety concerns of using this product. However, The American Society of Retina Specialists has published online safety information about compounding pharmacies to help retina specialists choose high-quality providers of bevacizumab. The FDA has Draft Guidance regarding drug compounding and repackaging of biologics to further standardize quality of bevacizumab. Furthermore, a 2015 study comparing injections of bevacizumab and injections of aflibercept, found that compounded bevacizumab was not linked to a higher risk of eye infection versus those treated with aflibercept. Rates of serious eye infection were 0.017 percent for compounded bevacizumab and 0.025 percent for aflibercept.
- Retina specialists are responsible for the quality and safety of any compounded drug that they administer to a patient. The AAO has the following recommendations for sourcing bevacizumab:
    - Select a compounding pharmacy accredited by the PCAB, which adheres to quality standards for aseptic compounding of sterile medications (USP <797>). Please note: PCAB does not track or keep record of specific medications that a pharmacy can compound.
    - Record the lot numbers of the medication in the patient's record and in a logbook or spreadsheet in case the numbers are needed for tracking later.
- For payment guidance for bevacizumab given via intravitreal injection see payment policy 97.0 Compound Drugs Administered in the Physician's Office
- Aflibercept (Eylea® HD) is a higher dose (HD) version of Eylea® that reduces injection frequency. It has the same mechanism of action as Eylea®. The approval of Eylea® HD was based on the 48-week results of the Phase 3, double-masked, active-controlled PULSAR and PHOTON trials which compared Eylea® HD to Eylea® 2 mg (marketed as Eylea®) in wAMD and DME, respectively. Both trials met their primary endpoint, with Eylea® HD demonstrating noninferiority in best corrected visual acuity (BCVA) with both 12- and 16-week dosing regimens in wAMD and DME, compared with Eylea® (given as an 8-week dosing regimen after initial monthly doses).

Table 1: Recommended Dosing Regimen

Drug	Indication	Dosing Regimen
Brolucizumab (Beovu®)	AMD	6 mg (0.05 mL of 120 mg/mL solution) monthly (approximately every 25-31 days) for the first three doses, followed by 6 mg (0.05 mL) by intravitreal injection once every 8-12 weeks

Drug	Indication	Dosing Regimen
	DME	6 mg (0.05 mL of 120 mg/mL solution) every six weeks (approximately every 39-45 days) for the first five doses, followed by one dose of 6 mg (0.05 mL of 120 mg/mL solution) by intravitreal injection every 8-12 week
Ranibizumab (Lucentis®) Ranibizumab-eqrn (Cimerli®)	AMD	0.5 mg (0.05 mL of a 10 mg/mL solution) once a month (about every 28 days) **Alternative dosing:** Once monthly injections for three months followed by 4-5 doses dispersed among the following nine months Or Treatment may be reduced to one injection every three months' after the first 4 injections if monthly injections are not feasible
	RVO	0.5 mg (0.05 mL of a 10 mg/mL solution) every 28 days
	DME or DR	0.3 mg (0.05 mL of 6 mg/ml solution) every 28 days
	mCNV	0.5 mg (0.05 mL of a 10 mg/mL ranibizumab solution) once a month for up to 3 months; may retreat if needed
Aflibercept (Eylea®) Aflibercept-ayyh (Pavblu®)	AMD	2 mg (0.05 mL) once a month for three months then once every two months. Some patients may need every four weeks (monthly) dosing after the first 12 weeks (three months). Although not as effective as the recommended every eight week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy
	RVO	2 mg (0.05 mL) once a month
	DME or DR	2 mg (0.05 mL) once a month for five months then once every two months
	ROP (Eylea® only indication)	0.4mg (0.01 mL or 10 microliters). Treatment interval between doses in same eye should be at least 10 days
Aflibercept (Eylea® HD)	AMD	8mg (0.07 mL) once a month for the first three doses, followed by 8 mg (0.07 mL) once every 8 to 16 weeks, +/- 1 week
	DME or DR	8mg (0.07 mL) once a month for the first three doses, followed by 8 mg (0.07 mL) once every 8 to 16 weeks, +/- 1 week
Ranibizumab (Susvimo®)	AMD	2 mg (0.02 mL of 100mg/mL solution) continuously delivered via the Susvimo® ocular implant with refills administered every 24 weeks (approximately six months)
	AMD	Once a month

Drug	Indication	Dosing Regimen
Ranibizumab-nuna (Byooviz®)	RVO	Once a month
	mCNV	Once a month
Faricimab (Vabysmo®)	AMD	6 mg (0.005 mL of 120 mg/mL solution) every four weeks for the first four doses. Additional efficacy was not demonstrated when dosed every four weeks compared to every eight weeks, some patients may need every four weeks (monthly) dosing after the first four doses.
	DME	1). 6 mg (0.05 mL of 120 mg/mL solution) administered every four weeks for at least four doses. If resolution of edema, can be dosed every four weeks or every eight weeks 2). 6 mg dose every eight weeks Additionally, efficacy was not demonstrated in most patients when dosed every four weeks compared to every eight weeks, some patients may need every four weeks dosing after the first doses.

Table 2. Indications

Drug	AMD	RVO	DME	DR	mCNV	ROP
Bevacizumab (Avastin®)	X**	X**	X**	X**		
Brolucizumab (Beovu®)	X		X			
Ranibizumab (Lucentis®)	X	X	X	X	X	
Ranibizumab-eqrn (Cimerli®)	X	X	X	X	X	
Ranibizumab-nuna (Byooviz®)	X	X			X	
Ranibizumab (Susvimo®)	X					
Aflibercept (Eylea®)	X	X	X	X		X
Aflibercept (Pavblu®)	X	X	X	X		
Aflibercept (Eylea® HD)	X		X	X		
Pegaptanib (Macugen®)*	X					
Faricimab (Vabysmo®)	X		X			

*Discontinued marketing status as per the FDA; **Off-label FDA Uses

AMD: Neovascular (Wet) Age-related Macular Degeneration; **RVO**: Macular Edema Following Retinal Vein Occlusion; **DME**: Diabetic Macular Edema; **DR**: Diabetic Retinopathy; **mCNV**: Myopic choroidal Neovascularization; **ROP**: Retinopathy of Prematurity

Table 3: List of Covered Diagnoses and Synonyms

Covered 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)
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
Myopic choroidal neovascularization	• Choroidal neovascularization secondary to pathologic myopia (mCNV)
Retinopathy of prematurity	• Retrolental firoplasia (RLF) • Terry syndrome

Table 4: Preferred Products

Preferred Products – No Prior Authorization Required
Bevacizumab (Avastin®)
Aflibercept (Eylea®)
Aflibercept-ayyh (Pavblu®)
Ranibizumab (Lucentis®)
Ranibizumab-nuna (Byooviz®)
Ranibizumab-eqrn (Cimerli®)
Non-Preferred Products – Prior Authorization/Step Therapy Required
Aflibercept (Eylea® HD)
Faricimab (Vabysmo®)

Brolucizumab (Beovu®)
Ranibizumab (Susvimo®)

Table 5: BILLING GUIDELINES AND CODING:

Preferred Products – No Prior Authorization Required		
Drug CODES*		
HCPCS	J0178	Injection, aflibercept, 1 mg (Eylea)
	J2778	Injection, ranibizumab, 0.1 mg (Lucentis)
	J7999	Compounded drug, not otherwise classified (Bevacizumab)
	Q5124	Injection, ranibizumab-nuna, biosimilar, (Byooviz), 0.1 mg
	Q5128	Injection, ranibizumab-eqrn (Cimerli), biosimilar, 0.1 mg
	Q5147	Injection, aflibercept-ayyh (pavblu), biosimilar, 1 mg
Non-Preferred Products – Prior Authorization/Step Therapy Required		
	J0177	Injection, aflibercept hd, 1 mg (Eylea HD)
	J0179	Injection, brolucizumab-dbll, 1 mg (Beovu)
	J2777	Injection, faricimab-svoa, 0.1 mg (Vabysmo)
	J2779	Injection, ranibizumab, via intravitreal implant (Susvimo), 0.1 mg
Administration Codes*		
CPT	67028	Injection eye drug
Modifiers	-50	Bilateral procedure
	-LT	Left eye
	-RT	Right eye

*Coding Notes:
• The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
• HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES:

1. Eylea package insert. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2023 Feb.
2. Lucentis package insert. South San Francisco, CA: Genentech Inc.; 2020 October.
3. Susvimo package insert. South San Francisco, CA: Genentech Inc.; 2022 April.
4. Vabysmo package insert. South San Francisco, CA: Genentech Inc.; 2022 February.

5. Cimerli package insert. Redwood City, CA: Coherus BioSciences, Inc.; 2022 August.
6. Bevacizumab. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
7. Arroyo JG. Age-related macular degeneration: Treatment and prevention. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on November 29, 2017.)
8. American Academy of Ophthalmology-Preferred Practice Patterns (AAO-PPP) Retina/Vitreous Panel, Hoskins Center for Quality Eye Care. Age-Related Macular Degeneration PPP – Update 2015. Jan 2015.
9. American Academy of Ophthalmology-Preferred Practice Patterns (AAO-PPP) Retina/Vitreous Panel, Hoskins Center for Quality Eye Care. Diabetic Retinopathy PPP – Update 2016. Feb 2016.
10. Ranibizumab versus Bevacizumab to Treat Neovascular Age-related Macular Degeneration: One-Year Findings from the IVAN Randomized Trial. The IVAN Study Investigators, Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, Reeves BC. Ophthalmology. 2012;7:1399-1411.
11. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, et al. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration: Two-Year Results. Ophthalmology; 2012;7:1388-98.
12. SD Solomon et al. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database Syst Rev 2014 Aug 29; 8:CD005139.
13. The Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015 Feb 18.
14. [Beovu®] package insert. East Hanover, NJ: Novartis Pharmaceutical Corporation. May 2021
15. Dugel PU, Koh A, Ogura Y, et al.: HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. Ophthalmology. 2019; pii: S0161-6420(18)33018-5. 10.1016/j.ophtha.2019.04.017
16. FDA approved first biosimilar to treat macular degeneration disease and other eye conditions. U.S. Food & Drug Administration. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-biosimilar-treat-macular-degeneration-disease-and-other-eye-conditions. (Accessed on April 24, 2022).