Policy Name	Clinical Policy – Vascular Endothelial Growth Factor Inhibitors (Anti-VEGF)
Policy Number	1317.00
Department	Clinical Product & Development
Subcategory	Medical Management
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Company Entities Supported (Select All that Apply):
X Superior Vision Benefit Management
X Superior Vision Services
X Superior Vision of New Jersey, Inc.
X Block Vision of Texas, Inc. d/b/a Superior Vision of Texas
X Davis Vision
(Collectively referred to as 'Versant Health' or 'the Company')

Acronyms and Definitions	
ACSC	Acute central serous choroidopathy
ANG-2	Angiopoietin-2
ARMD	Age related macular degeneration
A-VEGF or Anti-VEGF	Anti-Vascular Endothelial Growth Factor
Biologics/Biologicals	Biologics, or biologicals, are large, living molecules, developed to disrupt or replace an adverse biological reaction within living organisms. Biologics vary from chemical formulations in that they interact biologically instead of chemically to induce a therapeutic change. The original form of a biologic pharmaceutical is called the innovator biologic or the reference medicine.
Biosimilars	Biosimilars are molecules with similarity to existing biologic or biological pharmaceuticals defined as the reference medicine. Biosimilars strive to have comparable pharmacokinetics, pharmacodynamics, immunogenicity, safety, and efficacy to the reference medicine to establish biosimilarity.
BRVO	Branch retinal vein occlusion
CCSC	Chronic Central serous Choroidopathy
CIME	Center (or central) Involved DME
CME	Cystoid macular edema
CNV	Choroidal neovascularization
CRVO	Central retinal vein occlusion
CSME	Clinically significant macular edema

DME	Diabetic macular edema
DR	Diabetic retinopathy
IVFA	Intravenous fluorescein angiogram
MEfRVO	Macular edema from retinal vein occlusion
NPDR	Non proliferative diabetic retinopathy
NV	Neovascularization/neovascular
NVD/NVE	Neovascularization of the disc/ elsewhere
PDR	Proliferative diabetic retinopathy
POHS	Presumed ocular histoplasmosis syndrome
ROP	Retinopathy of Prematurity
RVO	Retinal vein occlusion
Step Therapy	A pharmaceutical benefit design that specifies medications, often generic formulations, to be trialed prior to using the more expensive medications or formulations. Step therapy requires that different types of medications are tried in successive stages rather than strictly requiring generic substitution.
VMT	Vitreomacular traction

PURPOSE

To provide the medical necessity criteria to support the indication(s) of intravitreal injections (other than antibiotics and corticosteroids). Applicable procedure codes are also defined.

POLICY

A. Background

This policy does not apply to children under one year of age with diagnosis of retinopathy of prematurity (ROP).

This clinical policy addresses the use of intravitreal vascular endothelial growth factor inhibitors. These medications have demonstrated efficacy for many chorioretinal, and retinal vascular disorders including:

1. Diabetic retinopathy and diabetic macular edema[1]
2. Retinal venous occlusive disease[2]
3. Choroidal neovascularization[3]
4. Exudative macular degeneration[4]
5. Macular edema associated with retinal arterial macro aneurysms[5] or radiation retinopathy[6]
6. Retinopathy of prematurity[7]
7. Neovascular glaucoma[8] or other causes of retinal neovascularization[9]

[1] Bhandari, 2020
[2] Avery, 2017, Nicolo, 2021
[3] Russell, 2019.
[4] Ammar, 2020
[5] Speilburg, 2014.
[6] Zamber, 1993,
[7] Bashour, 2015
[8] Nieves, 2022
[9] D'Amore, 1994.

B. Vascular Endothelial Growth Factor Inhibitors (Anti-VEGF)

Vascular Endothelial Growth Factor Inhibitors (anti-VEGF) suppress the progression of macular edema (ME) and neovascularization of the retina (NV) and choroid (CNV). These agents currently include pegaptanib (Macugen), bevacizumab (Avastin), bevacizumab-adcd (Vegzelma), ranibizumab (Lucentis/Cimerli), ranibizumab-nuna (Byooviz), aflibercept (Eylea), brolucizumab (Beovu), and ranibizumab PDS 100-mg/ml (Susvimo). Currently, Beovu is approved for treating exudative macular degeneration and diabetic macular edema.

1. Medical necessity may be demonstrated for anti-VEGF drugs by the applicable diagnosis in Tables 1 and 2.

2. Documentation requirements for Anti-VEGF intravitreal injections may be requested to support the above conditions. Legible clinical records are required, including:

    a. An examination of the anterior segment and posterior segment with documented pertinent findings; and,
    b. The interpretation and report from diagnostic studies performed, including ophthalmic computed tomography (OCT) or fluorescein angiogram or fundus photograph; and,
    c. Clinical plan of care to include the following specifics of patient condition:
        i. Comparative data (e.g., is the condition improving, deteriorating or unchanged); and,
        ii. Clinical management; and,
        iii. The impression/plan which must state the specific anti-VEGF to be used; and
        iv. Documentation of when the previous anti-VEGF was administered to either the right and/or left eye.

C. Combination Vascular Endothelial Growth Factor Inhibitors (Anti-VEGF) and Angiopoietin-2 (Ang-2) Inhibitors

Vabysmo (faricimab-svoa) is a dual inhibitor working on two different molecular targets. It acts as a vascular endothelial growth factor (A-VEGF) and angiopoietin-2 (Ang-2) inhibitor. Medical necessity may be demonstrated by the diagnosis of neovascular (wet) age-related macular degeneration (nAMD), or diabetic macular edema (DME), or macular edema due to retinal vein occlusion (MEfRVO).

D. Step Therapy

The step therapy criteria apply only to patient populations who are required per the client health plan to be managed on a step therapy protocol, as.

1. The request for pegaptanib (Macugen), ranibizumab (Lucentis), ranibizumab-nuna (Byooviz), aflibercept (Eylea), ranibizumab PDS (Susvimo), faricimab-sova (Vabysmo) or brolucizumab (Beovu) must demonstrate failure or intolerance to a trial of bevacizumab (Avastin) injections or its biosimilars.
2. Therapy failure and intolerance is defined and documented in the medical record.
3. Patients who are currently treated with either Beovu, Byooviz, Cimerli, Eylea, Lucentis, Macugen, or Vabysmo may continue these agents [10],[11],[12].
4. Patients who are currently treated with either Beovu, Byooviz, Cimerli, Eylea, Lucentis, Macugen, or Vabysmo may continue these agents [13],[14],[15].

[10] Heier 2012
[11] Rayess, 2015
[12] Bressler 2019
[13] Heier 2012
[14] Rayess, 2015
[15] Bressler 2019

Table 1 of 2

Diagnosis	Avastin bevacizumab and biosimilars: Vegzelma (bevacizumab - adcd) Alymsys (bevacizumab - maly), MVASI (bevacizumab - awwb), ZIRABEV (bevacizumab - bvzr)	Beovu brolucizumab	Eylea Aflibercept and biosimilars Ahzantive (aflibercept-mrbb) Enzeevu™ (aflibercept-abzv) Yesafili (aflibercept -jbvf) Opuviz (aflibercept-yszy) Pavblu (aflibercept-ayyh)	Eylea HD aflibercept	Macugen pegaptanib
Angioid streaks with CNV	X				
Choroiditis with CNV	X				
Degenerative myopia with CNV	X				
Diabetic macula edema (DME)	X	X	X	X	
Exudative retinopathy with CNV	X				
Exudative (Wet) AMD	X	X	X	X	X
Macular edema associated with retinal arterial macroaneurysms	X				
Macular edema due to RVO (MEfRVO)	X		X		
Non proliferative diabetic retinopathy without DME	X		X	X	
POHS with CNV	X				
Proliferative diabetic retinopathy	X		X	X	

Proliferative nondiabetic retinopathy	X				
Radiation retinopathy with or without CNV	X				
Retinal neo-vascularization	X				
RVO with ischemia, or NV	X		X		
Retinopathy of prematurity (ROP)[16]	X		X		
Rubeosis iridis with NV glaucoma	X				
Traumatic maculopathy with CNV	X				

Table 2 of 2

Diagnosis	Lucentis ranibizumab and biosimilars Cimerli (ranibizumab -eqrn) and BYOOVIZ (ranibizumab -nuna)	VABYSMO (faricimab -svoa)
Diabetic macula edema	X	X
Degenerative Myopia with CNV	X	
Exudative (Wet) AMD	X	X
Macular edema due to RVO (MEfRVO)	X	X[17]
Non proliferative diabetic retinopathy without DME	X	
POHS with CNV	X	
Proliferative nondiabetic retinopathy	X	
Proliferative diabetic retinopathy	X	
Retinopathy of prematurity	X (no biosimilar ROP use)	
RVO with ischemia or NV	X	

[16] Jung, 2023. Case study for biosimilar use in pediatric ROP. No FDA approvals have occurred for any biosimilar use for ROP diagnoses.
[17] FDA, 10/27/2023

E. Documentation

Medical necessity must be supported by adequate and complete documentation in the patient's medical record that describes the procedure and the medical rationale for it as in requirements above. All items must be available upon request to initiate or sustain previous payments. For any retrospective review, a full operative report and medical plan of care is required.

Every page of the record must be legible and include appropriate patient identification information (e.g., complete name, date(s) of service). Services provided/ordered must be authenticated by the physician, in a handwritten or electronic signature. Stamped signatures are not acceptable.

F. Procedural Details

CPT / HCPCS Codes	
67028	Intravitreal injection of a pharmacological agent (separate procedure)
C9399	Unclassified drugs or biologics Enzeevu™ (aflibercept-abzv), Opuviz (aflibercept-yszy), Pavblu (aflibercept -ayyh), and Yesafili (aflibercept -jbvf).
J0177	Injection, Eylea HD aflibercept 8 mg
J0178	Injection, aflibercept, 1 mg (Eylea)
J0179	Injection, brolucizumab -dbll, 1 mg. (Beovu)
J2503	Injection, pegaptanib sodium, 0.3 mg. (Macugen)
J2777	Injection, faricimab -svoa, 0.1 mg (Vabysmo)
J2778	Injection, ranibizumab 0.1 mg. (Lucentis)
J3490	Unclassified drugs
J3590	Unclassified biologics including Ahzantive® (aflibercept-mrbb), Enzeevu™ (aflibercept-abzv), (Opuviz aflibercept-yszy), Pavblu (aflibercept -ayyh), and Yesafili (aflibercept -jbvf).
J7999	Compounded drug, not otherwise classified
J9035	Injection, bevacizumab, 10 mg (Avastin) (Medicare A/B MAC jurisdictions H&L require code J7999 to be used for bevacizumab.)
Q5107	Injection, bevacizumab -awwb, biosimilar (MVASI) 10 mg.
Q5118	Injection, bevacizumab -bvzr, biosimilar, (ZIRABEV), 10 mg)
Q5124	Injection, ranibizumab -nuna, biosimilar, (Byooviz), 0.1 mg
Q5126	Injection, bevacizumab -maly, biosimilar, (Alymsys), 10 mg
Q5128	Injection, ranibizumab -eqrn (Cimerli), biosimilar, 0.1 mg
Q5129	Injection, bevacizumab -adcd (Vegzelma), biosimilar 10 mg
Required modifiers for 67028	
RT	Right side
LT	Left side
50	Bilateral
JW or JZ[18]	Drug waste or no drug waste

[18] CMS National Coverage Policy A55932. Feb 2023.

Invalid modifiers	
24	Unrelated Evaluation and Management Service by the Same Physician or Other Qualified Health Care Professional During a Postoperative Period
25	Significant, Separately Identifiable Evaluation and Management Service by the Same Physician or Other Qualified Health Care Professional on the Same Day of the Procedure or Other Service
26	Professional Component
57	Decision for Surgery
95	Telemedicine
TC	Technical Component

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RELATED POLICIES	
1345	Verteporfin Photodynamic Therapy
1346	Corticosteroid Implants and Injections

Document History		
Approval Date	***Revisions***	***Effective Date***
02/06/2018	Initial Policy	02/06/2018
03/13/2019	Annual review; no criteria changes.	03/13/2019
10/18/2019	Major revisions include step therapy indications for anti-VEGF agents and new medication Yutiq.	01/01/2020
12/18/2019	Addition of new FDA approved drug Beovu; correction of codes J7311, J2778, J7312.	01/01/2020
06/03/2020	Annual review; deletion of criteria for infant and pediatric retinopathy of prematurity.	12/01/2020
04/07/2021	Annual review; deletion of photodynamic therapy criteria (J3396); anti-VEGF criteria stated as only applicable as step therapy protocol; add exudative macular degeneration as an indication for anti-VEGF; add off label use of Retisert for diabetic macular edema; add use of Yutiq for diabetic macular edema; add criteria of macular hole of at least 400 microns for Jetrea; add restriction of Jetrea to single treatment.	09/01/2021
01/05/2022	Retitled to Vascular Endothelial Growth Factor Inhibitors (Anti-VEGF). Removed corticosteroids and Jetrea ocriplasmin to separate policies. Added drugs Byooviz and Susvimo with related criteria.	07/01/2022
01/04/2023	Annual review; clarify Anti-VEGF is for both chorioretinal and retinal vascular disorders; delete recalled implant system Susvimo; for conditions meeting medical necessity, removed specifying tests, measurements; for step therapy, removed strict requirement for three trials, and deleted definitions of failure which are substantiated in the medical record. For Avastin/bevacizumab added indications of NPDR and PDR; for Vabysmo/faricimab-svoa added indication of wet AMD, removed replaced CPT code C9097; added/updated CPT codes for Cimerli, Vabysmo and Byooviz.	07/01/2023
07/12/2023	Expanded/corrected diagnoses list for A-VEGF drugs Beovu and Eylea; add fundus photo as option for diagnostic study; expanded exceptions to step therapy; added new biosimilar Vegzelma.	01/01/2024
01/03/2024	Add 3 Avastin biosimilar formulations; add new Eylea HD formulation and its indications; add indication of MEfRVO to Eylea and Vabysmo; add JZ modifier.	05/01/2024
07/10/2024	Add 2 aflibercept biosimilars; update Eylea HD to permanent HCPCS code J0177.	10/01/2024
01/08/2025	Add three new aflibercept biosimilars. For pediatric ROP condition: reduce # of drugs allowed from all drugs to: Avastin + biosimilars, Eylea + biosimilars, and Lucentis with no biosimilars.	05/01/2025

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