

<b>Policy Name</b>	Clinical Policy – Vascular Endothelial Growth Factors (Anti-VEGF)
<b>Policy Number</b>	1317.00
<b>Department</b>	Clinical Product & Strategy
<b>Subcategory</b>	Medical Management
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**Company Entities Supported (Select All that Apply):**

- Superior Vision Benefit Management  
 Superior Vision Services  
 Superior Vision of New Jersey, Inc.  
 Block Vision of Texas, Inc. d/b/a Superior Vision of Texas  
 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 requires certain specified 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 one year or less 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
2. Retinal venous occlusive disease
3. Choroidal neovascularization
4. Exudative macular degeneration
5. Macular edema associated with retinal arterial macro aneurysms.
6. Macular edema associated with radiation retinopathy.
7. Retinopathy of Prematurity
8. Neovascular glaucoma
9. Other causes or retinal neovascularization

### 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 <sup>1,2,3</sup>.

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<sup>1</sup> Heier 2012

<sup>2</sup> Rayess, 2015

<sup>3</sup> Bressler 2019

<b>Table 1 of 2</b>					
<b>Diagnosis</b>	<b>Avastin bevacizumab and biosimilars: Vegzelma bevacizumab- adcd Almysys bevacizumab- maly, MVASI bevacizumab- awwb, ZIRABEV bevacizumab-bvzr</b>	<b>Beovu brolucizumab</b>	<b>Eylea aflibercept</b>	<b>Eylea HD aflibercept</b>	<b>Macugen pegaptanib</b>
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				

<b>Table 1 (cont.)</b>					
Radiation retinopathy with or without CNV	<b>X</b>				
Retinal neo-vascularization	<b>X</b>				
RVO with ischemia, or NV	<b>X</b>		<b>X</b>		
Retinopathy of prematurity (ROP)	<b>X</b>		<b>X</b>		
Rubeosis iridis with NV glaucoma	<b>X</b>				
Traumatic maculopathy with CNV	<b>X</b>				

<b>Table 2 of 2</b>		
<b>Diagnosis</b>	<b>Lucentis ranibizumab and biosimilars Cimerli ranibizumab-eqrn and BYOOVIZ ranibizumab-nuna</b>	<b>VABYSMO faricimab-svoa</b>
Diabetic macula edema	<b>X</b>	<b>X</b>
Degenerative Myopia with CNV	<b>X</b>	
Exudative (Wet) AMD	<b>X</b>	<b>X</b>
Macular edema due to RVO (MEfRVO)	<b>X</b>	<b>X<sup>4</sup></b>
Non proliferative diabetic retinopathy without DME	<b>X</b>	
POHS with CNV	<b>X</b>	
Proliferative nondiabetic retinopathy	<b>X</b>	
Proliferative diabetic retinopathy	<b>X</b>	
RVO with ischemia or NV	<b>X</b>	

<sup>4</sup> 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

<b>CPT / HCPCS Codes</b>	
67028	Intravitreal injection of a pharmacological agent (separate procedure)
C9161	Injection, aflibercept HD, 1 mg (Eylea HD)
C9399	Unclassified drugs or biologics
J0178	Injection, aflibercept, 1 mg (Eylea)
J0179	Injection, brolucizumab-dbl, 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
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
<b>Required modifiers for 67028</b>	
RT	Right side
LT	Left side
50	Bilateral
JW or JZ <sup>5</sup>	Drug waste or no drug waste

<sup>5</sup> CMS National Coverage Policy A55932. Feb 2023.

<b>Invalid modifiers</b>	
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
57	Decision for Surgery
26	Professional Component
TC	Technical Component
95	Telemedicine

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<b>RELATED POLICIES</b>	
1345	Verteporfin Photodynamic Therapy
1346	Corticosteroid Implants and Injections
1347	Jetrea ocriplasmin (retired)

<b>Document History</b>		
<b>Approval Date</b>	<b>Revisions</b>	<b>Effective Date</b>
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

<b>REFERENCES AND SOURCES</b>
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1. Ba J, Peng RS, Xu D, et al. Intravitreal anti-VEGF injections for treating wet age-related macular degeneration: a systematic review and meta-analysis. *Drug Des Devel Ther.* 2015; 9:5397-5405. PMID 26451092
2. Baker CW, Glassman AR, Wesley MR, et al. Effect of Initial Management with Aflibercept Laser Photocoagulation vs Observation on Vision Loss Among Patients with Diabetic Macular Edema Involving the Center of the Macula and Good Visual Acuity; A Randomized Clinical Trial; *JAMA* May 21, 2019, Volume 321, Number 19.
3. Bakri SJ, Thorne JE, Ho AC, et al. Safety and efficacy of anti-vascular endothelial growth factor therapies for Neo vascular age-related macular degeneration: a report by the American Academy of Ophthalmology. 2019; 126(1):55-63. Doi: 10.1016/j.optha.2018.07.028.



4. Bakri SJ, Wolfe JD, Regillo CJ, et al. Evidence-Based Guidelines for Management of Diabetic Macular Edema Journal of Vitreo Retinal Diseases 1-8<sup>a</sup> The Author(s) 2019 Article reuse guidelines: [sagepub.com/journals-permissions](https://sagepub.com/journals-permissions) DOI: 10.1177/2474126419834711.
5. Bashour M, Menassa J, Gerontis CC. Retinopathy of Prematurity Ophthalmologic Approach Medication Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreal ranibizumab for proliferative diabetic retinopathy: A randomized trial. *JAMA* 2015; 314:20:2137-2146.
6. Bauml CR, Sørensen TL, Karcher H, et.al. Efficacy and safety of brolucizumab in age-related macular degeneration: A systematic review of real-world studies. *Acta Ophthalmol.* 2023 Mar;101(2):123-139. doi: 10.1111/aos.15242. Epub 2022 Sep 18. PMID: 36117281.
7. Bauml CR, Spaide RF, Vajzovic L, et.al. Retinal Vasculitis and Intraocular Inflammation after Intravitreal Injection of Brolucizumab. *Ophthalmology.* 2020 Oct;127(10):1345-1359. doi: 10.1016/j.ophtha.2020.04.017. Epub 2020 Apr 25. PMID: 32344075.
8. Bhandari S, Nguyen V, Fraser-Bell S, et.al. Ranibizumab or Aflibercept for Diabetic Macular Edema: Comparison of 1-Year Outcomes from the Fight Retinal Blindness! Registry. *Ophthalmology.* 2020 May;127(5):608-615. doi: 10.1016/j.ophtha.2019.11.018. Epub 2019 Nov 26. PMID: 31932092.
9. Bohni SC, Bittner M, Howell j; Bachmann et al. Comparison of Eylea with Lucentis as first-Line therapy in patients with treatment-naïve neovascular age-related macular degeneration, *BMC Ophthalmology* 15 August 2015 Article number: 109 (2015).
10. Bressler, NM, Odia, I, Maguire, M, et.al. DRCR Retina Network. Association between Changes in Visual Acuity and Change in Central Subfield Thickness During Treatment of Diabetic Macular Edema in Participants Randomized to Aflibercept, Bevacizumab, or Ranibizumab.” A post hoc analysis of the Protocol T Randomized Clinical Trial. *JAMA Ophthalmology*, Sept. 2019 Vol 137, 9.
11. Carrasco J, Pietsch GA, Nicolas MP, et.al. Real-World Effectiveness and Real-World Cost-Effectiveness of Intravitreal Aflibercept and Intravitreal Ranibizumab in Neovascular Age-Related Macular Degeneration: Systematic Review and Meta-Analysis of Real-World Studies. *Adv Ther.* 2020 Jan;37(1):300-315. doi: 10.1007/s12325-019-01147-6. Epub 2019 Nov 14. PMID: 31728825; PMCID: PMC6979459.
12. Chi SC, Kang YN, Huang YM. Systematic review with network meta-analysis of anti-vascular endothelial growth factor use in managing polypoidal choroidal vasculopathy. *Sci Rep.* 2021 Feb 2;11(1):2735. doi: 10.1038/s41598-021-82316-y. PMID: 33531615; PMCID: PMC7854625.
13. Clinical Review Report: Brolucizumab (Beovu): (Novartis Pharmaceuticals Canada Inc.): Indication: Treatment of Neovascular (wet) Age-Related Macular Degeneration (AMD) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 Jul. PMID: 33301280.
14. Deak GG, Schmidt-Erfurth UM, Jampol LM. Correlation of Central Retinal Thickness and Visual Acuity in Diabetic Macular Edema. *JAMA Ophthalmology* 136, 11, November 2018.
15. Downie LE, Makrai E, Bonggotgetsakul Y, et al. Appraising the Quality of Systematic Reviews for Age Related Macular Degeneration Interventions-A Systematic Review, *JAMA Ophthalmology* 2018 136(9); 1051-61.
16. Dugel PU, Koh A, Ogura Y, et.al. HAWK and HARRIER Study Investigators. HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. *Ophthalmology.* 2020 Jan;127(1):72-84. doi: 10.1016/j.ophtha.2019.04.017. Epub 2019 Apr 12. PMID: 30986442.
17. Finger RP, Daien V, Eldem BM, et.al. J. Anti-vascular endothelial growth factor in neovascular age-related macular degeneration - a systematic review of the impact of anti-VEGF on patient outcomes and healthcare systems. *BMC Ophthalmol.* 2020 Jul 17;20(1):294. doi: 10.1186/s12886-020-01554-2. PMID: 32680477; PMCID: PMC7368708.
18. Finger RP, Dennis N, Freitas R, et.al. Comparative Efficacy of Brolucizumab in the Treatment of Neovascular Age-Related Macular Degeneration: A Systematic Literature Review and Network Meta-Analysis. *Adv Ther.* 2022 Aug;39(8):3425-3448. doi: 10.1007/s12325-022-02193-3. Epub 2022 Jun 9. PMID: 35678996; PMCID: PMC9309118.
19. Garweg JG. A Randomized, Double-Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Patients with Visual Impairment due to Diabetic Macular

- Edema (KITE). 2020 Apr;237(4):450-453. English. doi: 10.1055/a-1101-9126. Epub 2020 Mar 4. PMID: 32131127.
20. Hang A, Feldman S, Amin AP, et.al. Intravitreal Anti-Vascular Endothelial Growth Factor Therapies for Retinal Disorders. Pharmaceuticals (Basel). 2023 Aug 11;16(8):1140. doi: 10.3390/ph16081140. PMID: 37631054; PMCID: PMC10458692.
  21. Hariprasad SM, Gale RP, Weng CY, et.al. An Introduction to Biosimilars for the Treatment of Retinal Diseases: A Narrative Review. Ophthalmol Ther. 2022 Jun;11(3):959-982. doi: 10.1007/s40123-022-00488-w. Epub 2022 Mar 12. PMID: 35278204; PMCID: PMC9114261.
  22. Holekamp NM. Review of Neovascular Age-Related Macular Degeneration Treatment Options Am J Manag Care. 2019; 25: -S0. <https://www.asrs.org/asrs-community/pat-survey>.
  23. Hykin P, Prevost T, Vasconcelos JC, et al. Clinical Effectiveness of Intravitreal Therapy with Ranibizumab vs Aflibercept vs Bevacizumab for Macular Edema Secondary to Central Retinal Vein Occlusion. JAMA Ophthalmol. Published online August 29, 2019. doi:10.1001/jamaophthalmol.2019.3305.
  24. Khan M, Aziz AA, Shafi NA, et.al. (August 2020). "Targeting Angiopoietin in Retinal Vascular Diseases: A Literature Review and Summary of Clinical Trials Involving Faricimab". Cells. 9 (8): 1869. doi:10.3390/cells9081869. PMC 7464130. PMID 32785136.
  25. Kuo BL, Singh RP. Brolucizumab for the treatment of diabetic macular edema. Curr Opin Ophthalmol. 2022 May 1;33(3):167-173. doi: 10.1097/ICU.0000000000000849. Epub 2022 Mar 9. PMID: 35266896.
  26. Kutlutürk Karagöz I, Allahverdiyev A, Bağirova M, et.al. Current Approaches in Treatment of Diabetic Retinopathy and Future Perspectives. J Ocul Pharmacol Ther. 2020 Sep;36(7):487-496. doi: 10.1089/jop.2019.0137. Epub 2020 May 21. PMID: 32453671.
  27. Liberski S, Wichrowska M, Kocięcki J. Aflibercept versus Faricimab in the Treatment of Neovascular Age-Related Macular Degeneration and Diabetic Macular Edema: A Review. Int J Mol Sci. 2022 Aug 20;23(16):9424. doi: 10.3390/ijms23169424. PMID: 36012690; PMCID: PMC9409486.
  28. Mansour SE, Browning DJ, Wong K, et.al. The Evolving Treatment of Diabetic Retinopathy. Clin Ophthalmol. 2020 Mar 4; 14:653-678. doi: 10.2147/OPTH.S236637. PMID: 32184554; PMCID: PMC7061411.
  29. Nguyen QD, Das A, Do DV, et.al. Brolucizumab: Evolution through Preclinical and Clinical Studies and the Implications for the Management of Neovascular Age-Related Macular Degeneration. Ophthalmology. 2020 Jul;127(7):963-976. doi: 10.1016/j.ophtha.2019.12.031. Epub 2020 Jan 17. PMID: 32107066.
  30. Nguyen V, Daien V, Guymer R. et al. Projection of long term visual acuity outcomes based upon initial treatment response in neovascular age related macular degeneration, Ophthalmology 2019;126:64-74.
  31. Nicolò M, Ferro Desideri L, Vagge A, et.al. Faricimab: an investigational agent targeting the Tie-2/angiopoietin pathway and VEGF-A for the treatment of retinal diseases. Expert Opin Investig Drugs. 2021 Mar;30(3):193-200. doi: 10.1080/13543784.2021.1879791. Epub 2021 Feb 4. PMID: 33471572.
  32. Ohno-Matsui K, Ikuno Y, Lai TYY, et.al. Diagnosis and treatment guideline for myopic choroidal neovascularization due to pathologic myopia. Prog Retin Eye Res. 2018 Mar; 63:92-106. doi: 10.1016/j.preteyeres.2017.10.005. Epub 2017 Oct 28. PMID: 29111299.
  33. Okada M, Wong TY, Mitchell P, et.al. Defining Nonadherence and Non persistence to Anti-Vascular Endothelial Growth Factor Therapies in Neovascular Age-Related Macular Degeneration. JAMA Ophthalmol. 2021 Jul 1;139(7):769-776. doi: 10.1001/jamaophthalmol.2021.1660. Erratum in: JAMA Ophthalmol. 2021 Sep 23: null. PMID: 34081099; PMCID: PMC8176386.
  34. Peto T, Chakravarthy U. New Findings from Diabetic Retinopathy Clinical Research Retina Network Protocol V Confirm a Role for Focal Laser Photocoagulation or Observation for Eyes with Center-Involved Diabetic Macular Edema and Good Visual Acuity New Is Not Always Best, JAMA Ophthalmology 2018, 1876.
  35. Sadda SR, Guymer R, Monés JM, et.al Anti-Vascular Endothelial Growth Factor Use and Atrophy in Neovascular Age-Related Macular Degeneration: Systematic Literature Review and Expert Opinion. Ophthalmology. 2020 May;127(5):648-659. doi: 10.1016/j.ophtha.2019.11.010. Epub 2019 Nov 22. PMID: 32081493.

36. Sahni J, Dugel PU, Patel SS, et.al. Safety and Efficacy of Different Doses and Regimens of Faricimab vs Ranibizumab in Neovascular Age-Related Macular Degeneration: The AVENUE Phase 2 Randomized Clinical Trial. *JAMA Ophthalmol.* 2020 Sep 1;138(9):955-963. doi: 10.1001/jamaophthalmol.2020.2685. PMID: 32729888; PMCID: PMC7393587.
37. Sankar MJ, Sankar J, Chandra P. et.al. Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity; Systematic Review - Intervention Version published: 08 January 2018; <https://doi.org/10.1002/14651858.CD009734.pub3> .
38. Scott IU, Van Veldhuisen PC. Baseline Factors Associated with Six Month Visual Acuity and Retinal Thickness Outcomes in Patients with Macular Edema Secondary to Central Retinal Vein Occlusion or Hemi Retinal Vein Occlusion SCORE 2 Study Report Four, *JAMA Ophthalmology* 2017,135 (6), 639-49.
39. Sha W, Wen S, Chen L, et.al. The Role of SGLT2 Inhibitor in the Treatment of Diabetic Retinopathy. *J Diabetes Res.* 2020 Nov 12; 2020:8867875. doi: 10.1155/2020/8867875. PMID: 33274239; PMCID: PMC7676957.
40. Shalchi Z, Mahroo O, Bunce C, et.al. Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. *Cochrane Database Syst Rev.* 2020 Jul 7;7(7):CD009510. doi: 10.1002/14651858.CD009510.pub3. PMID: 32633861; PMCID: PMC7388176.
41. Sharma A, Kumar N, Kuppermann BD, Bandello F, Loewenstein A. Biotherapeutics and immunogenicity: ophthalmic perspective. *Eye (Lond).* 2019 Sep;33(9):1359-1361. doi: 10.1038/s41433-019-0434-y. Epub 2019 Apr 9. PMID: 30967643; PMCID: PMC7002711.
42. Sharma A, Kumar N, Parachuri N, et.al. Biosimilars for Retinal Diseases: An Update. *Am J Ophthalmol.* 2021 Apr; 224:36-42. doi: 10.1016/j.ajo.2020.11.017. Epub 2020 Dec 9. PMID: 33309691.
43. Sharma A, Reddy P, Kuppermann BD, et.al. Biosimilars in ophthalmology: "Is there a big change on the horizon?". *Clin Ophthalmol.* 2018 Oct 24; 12:2137-2143. doi: 10.2147/OPHTH.S180393. PMID: 30498330; PMCID: PMC6207386.
44. Sharma S, Khan MA, Chaturvedi A; RE-ENACT Study Investigators Group. Real-Life Clinical Effectiveness of Razumab® (the World's First Biosimilar of Ranibizumab) in Retinal Vein Occlusion: A Subgroup Analysis of the Pooled Retrospective RE-ENACT Study. *Ophthalmologica.* 2019;241(1):24-31. doi: 10.1159/000488602. Epub 2018 Jun 26. PMID: 29945143; PMCID: PMC6390449.
45. Siktberg, J., Kim, S.J., Sternberg, P. et al. Effectiveness of bevacizumab step therapy for neovascular age-related macular degeneration. *Eye* (2022). <https://doi.org/10.1038/s41433-022-02253-6>.
46. Sivaprasad S, Prevost AT, Vasconcelos JC, et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, noninferiority trial. *Lancet Lond Engl* 2017; 389:2193–2203.
47. Stahl A, Sukgen EA, Wu WC, et.al. FIREFLEYE Study Group. Effect of Intravitreal Aflibercept vs Laser Photocoagulation on Treatment Success of Retinopathy of Prematurity: The FIREFLEYE Randomized Clinical Trial. *JAMA.* 2022 Jul 26;328(4):348-359. doi: 10.1001/jama.2022.10564. PMID: 35881122; PMCID: PMC9327573.
48. Taher NO, Ghaddaf AA, Al-Ghamdi SA, et.al. Intravitreal Anti-vascular Endothelial Growth Factor Injection for Retinopathy of Prematurity: A Systematic Review and Meta-Analysis. *Front Med (Lausanne).* 2022 May 9; 9:884608. doi: 10.3389/fmed.2022.884608. PMID: 35615084; PMCID: PMC9124790.
49. Thulliez M, Angoulvant D, Pisella PG, et al. Overview of Systematic Reviews and Meta analyses on Systemic Adverse events associated With Intravitreal Anti–Vascular Endothelial Growth Factor Medication Use *JAMA Ophthalmology* 2018; 136(5):557-566.
50. Tong Y, Zhao KK, Feng D, et al. Comparison of the efficacy of anti-VEGF monotherapy versus PDT and intravitreal anti-VEGF combination treatment in AMD: a Meta-analysis and systematic review. *Int J Ophthalmol.* Aug 2016;9(7):1028-1037. PMID 27500113
51. Toto L, Di Antonio L, Costantino O, et.al. Anti-VEGF Therapy in Myopic CNV. *Curr Drug Targets.* 2021;22(9):1054-1063. doi: 10.2174/1389450122999210128180725. PMID: 33511955.
52. Tricco AC, Thomas SM, Lillie E, et.al. Anti-vascular endothelial growth factor therapy for age-related macular degeneration: a systematic review and network meta-analysis. *Syst Rev.* 2021 Dec 20;10(1):315. doi: 10.1186/s13643-021-01864-6. PMID: 34930439; PMCID: PMC8690960.

53. Vergmann AS, Grauslund J. Changes of visual fields in treatment of proliferative diabetic retinopathy: a systematic review. *Acta Ophthalmol.* 2020 Dec;98(8):763-773. doi: 10.1111/aos.14474. Epub 2020 May 18. PMID: 32421255.
54. Vujosevic S, Toma C, Villani E, et.al. Diabetic macular edema with neuro retinal detachment: OCT and OCT-angiography biomarkers of treatment response to anti-VEGF and steroids. *Acta Diabetol.* 2020 Mar;57(3):287-296. doi: 10.1007/s00592-019-01424-4. Epub 2019 Sep 21. PMID: 31541333.
55. Wells JA, Glassman AR, Ayala AR, et.al. Diabetic Retinopathy Clinical Research Network. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. *Ophthalmology.* 2016 Jun;123(6):1351-9. doi: 10.1016/j.ophtha.2016.02.022. Epub 2016 Feb 27. PMID: 26935357; PMCID: PMC4877252.
56. Yin X, He T, Yang S, et.al. Efficacy and Safety of AntiVascular Endothelial Growth Factor (Anti-VEGF) in Treating Neovascular Age-Related Macular Degeneration (AMD): A Systematic Review and Meta-analysis. *J Immunol Res.* 2022 Apr 15; 2022:6004047. doi: 10.1155/2022/6004047. PMID: 35465351; PMCID: PMC9033403.
57. Yoon CK, Oh J, Bae K, et.al. Efficacy and safety of a new ranibizumab biosimilar CKD-701 using a pro re nata treatment regimen in neovascular age-related macular degeneration: A phase 3 randomized clinical trial. *PLoS One.* 2022 Nov 14;17(11): e0275611. doi: 10.1371/journal.pone.0275611. PMID: 36374913; PMCID: PMC9662729.

## SOURCES

1. American Academy of Ophthalmology®. Diabetic Retinopathy PPP 2019. <https://www.aao.org/education/preferred-practice-pattern/diabetic-retinopathy-ppp>. Accessed 10/2023.
2. American Academy of Ophthalmology Preferred Practice Pattern: Age-related Macular Degeneration. PPP 2019. Hoskins Center for Quality Eye Care. <https://www.aao.org/education/preferred-practice-pattern/age-related-macular-degeneration-ppp>. Accessed 5/10/2023.
3. American Academy of Ophthalmology® Preferred Practice Pattern; Diabetic Retinopathy PPP 2019. Retina/Vitreous Committee, Hoskins Center for Quality Eye Care. <https://www.aao.org/education/preferred-practice-pattern/diabetic-retinopathy-ppp>. Accessed 10/2023.
4. American Academy of Ophthalmology®, Age-Related Macular Degeneration Preferred Practice Patterns. 2019. <https://www.aao.org/education/preferred-practice-pattern/age-related-macular-degeneration-ppp> Accessed 10/2023.
5. BEOVU Novartis Full Prescribing Information. [https://www.novartis.com/us-en/sites/novartis\\_us/files/beovu.pdf](https://www.novartis.com/us-en/sites/novartis_us/files/beovu.pdf). Accessed 10/2023.
6. BYOOVZ™ FDA full prescribing information. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/761202s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761202s000lbl.pdf). Accessed 10/2023.
7. CIMERLI Coding Reference Guide <https://www.cimerli.com/pdf/CIMERLI-Coding-Reference-Guide.pdf>. Accessed 10/2023.
8. CMS National Coverage Policy A55932. Billing and Coding: JW and JZ Modifier Billing Guidelines. Feb. 2023.
9. Eylea® aflibercept. FDA prescribing information. [https://www.regeneron.com/downloads/eylea\\_fpi.pdf](https://www.regeneron.com/downloads/eylea_fpi.pdf). Accessed 10/2023.
10. Eylea® HD aflibercept injection 8 mg. <https://eyleahcp.us/s/>. Accessed 10/2023.
11. Formycon Aflibercept biosimilar candidate FYB203 shows comparable efficacy to the reference product Eylea in Phase III study. <https://www.formycon.com/en/blog/press-release/formycons-aflibercept-biosimilar-kandidat-fyb203-zeigt-in-phase-iii-studie-vergleichbare-wirksamkeit-zum-referenzprodukt-eylea1/#:~:text=Aflibercept%20Biosimilar%20Candi>. Accessed 10/2023.
12. Iluvien® [package insert]. Alpharetta, GA; Alimera Sciences, Inc.; Accessed 10/2023.
13. NIH A type of ‘step therapy ‘ is an effective strategy for diabetic eye disease. 70% of eyes had been switched to Eylea after initial weeks of therapy but still had improvement. Cost savings worth the slowed progress. <https://www.nih.gov/news-events/news-releases/type-step-therapy-effective-strategy-diabetic-eye-disease>. Accessed 10/2023.
14. Retina Eye Doctor: Blog, re: Macugen use. <https://retinaeyedoctor.com/macugen-first-anti-vegf-eye-injection-so-wheres-waldo/>. Accessed 10/2023.

15. SUSVIMO © Recall 2023. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9887765/>. Accessed 10/2023.
16. VABYSMO™. FDA BLA 721235/S-003. Label Highlights of Prescribing information. Indications and Usage, Macular Edema Following Retinal Vein Occlusion (RVO). 10/2023. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2022/761235s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761235s000lbl.pdf) . Accessed 11/2023. Accessed 10/2023.
17. Vegzelma bevacizumab-adcd. FDA prescribing information. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2022/761268Orig1s000Correctedlbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761268Orig1s000Correctedlbl.pdf). Accessed 10/2023.