MASSACHUSETTS

Blue Cross Blue Shield of Massachusetts is an Independent Licensee of the Blue Cross and Blue Shield Association

Medical Policy

Intravitreal Angiogenesis Inhibitors for Retinal Vascular Conditions

Table of Contents

Policy Number: 401

BCBSA Reference Number: 9.03.27
NCD/LCD: NA

Related Policies

- Surgical Vision Services and Vision Training, #599
- Intravitreal Corticosteroid Implants, #272
- Intravitreal Angiogenesis Inhibitors for Choroidal Vascular Conditions, #343

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Intravitreal injection of **ranibizumab, bevacizumab or aflibercept** may be considered **MEDICALLY NECESSARY** for the treatment of the following retinal vascular conditions:

- Diabetic macular edema*
- Diabetic retinopathy*
- Macular edema following retinal vein occlusion*
- Retinopathy of prematurity
- Neovascular glaucoma
- Rubeosis (neovascularization of the iris).

Intravitreal injection of **ranibizumab, bevacizumab, or aflibercept** is considered **INVESTIGATIONAL** for the treatment of all other retinal vascular disorders.

Intravitreal injection of **pegaptanib** is considered **INVESTIGATIONAL** for treatment of retinal vascular disorders, including proliferative diabetic retinopathy, diabetic macular edema, and central or branch retinal vein occlusion.

* FDA approved indication (Lucentis and EYLEA).

Prior Authorization Information

Pre-service approval is required for all inpatient services for all products.

See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

	Outpatient
Commercial Managed Care (HMO and POS)	No
Commercial PPO and Indemnity	No
Medicare HMO Blue℠	No
Medicare PPO Blue℠	No

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
67028	Intravitreal injection of a pharmacologic agent (separate procedure)

HCPCS Codes

HCPCS codes:	Code Description
J0178	Injection, aflibercept, 1 mg
J2778	Injection, ranibizumab, 0.1 mg
J9035	Injection, bevacizumab, 10 mg

According to the policy statement above, the following HCPCS code is considered investigational for the conditions listed for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS Codes

HCPCS codes:	Code Description
J2503	Injection, pegaptanib sodium, 0.3 mg

Description

VEGF has been implicated in the pathogenesis of a variety of ocular vascular conditions characterized by neovascularization and macular edema. The macula, with the fovea at its center, has the highest photoreceptor concentration and is where visual detail is discerned. The anti-VEGF agents ranibizumab (Lucentis™), bevacizumab (Avastin®), pegaptanib (Macugen®) and aflibercept (EYLEA™) are used to treat choroidal neovascularization associated with age-related macular degeneration (AMD) and are being evaluated for the treatment of disorders of retinal circulation (eg, diabetic retinopathy, retinal vein occlusion, ROP).

For the treatment of ocular disorders, these agents are given by intravitreal injection every 1 to 2 months. Pegaptanib and ranibizumab bind extracellular VEGF to inhibit the angiogenesis pathway. Pegaptanib binds to the VEGF-165 isomer of VEGF-A while ranibizumab is an antibody fragment directed at all isoforms of VEGF-A. Bevacizumab is derived from the same murine monoclonal antibody precursor as ranibizumab, which binds to all isoforms of VEGF-A. Aflibercept (previously called VEGF Trap-Eye) is a recombinant fusion protein consisting of the VEGF binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin-G1. Aflibercept binds VEGF-A and placental growth factor, another angiogenic growth factor.

Diabetic Retinopathy

Diabetic retinopathy is a common microvascular complication of diabetes and a leading cause of blindness in adults. The two most serious complications for vision are DME and proliferative diabetic retinopathy. At its earliest stage (nonproliferative retinopathy), microaneurysms occur. With disruption of the blood-retinal barrier, macular retinal vessels become permeable, leading to exudation of serous fluid and lipids into the macula (macular edema). As the disease progresses, blood vessels that provide nourishment to the retina are blocked, triggering the growth of new and fragile blood vessels (proliferative retinopathy). Severe vision loss with proliferative retinopathy arises from vitreous hemorrhage. Moderate vision loss can also arise from macular edema (fluid accumulating in the center of the macula) during the proliferative or nonproliferative stages of the disease. Although proliferative disease is the main blinding complication of diabetic retinopathy, macular edema is more frequent and is the leading cause of moderate vision loss in people with diabetes.

Tight glycemic and blood pressure control is the first line of treatment to control diabetic retinopathy, followed by laser photocoagulation for patients whose retinopathy is approaching the high-risk stage. Although laser photocoagulation is effective at slowing the progression of retinopathy and reducing visual loss, it results in collateral damage to the retina and does not restore lost vision. Focal macular edema (characterized by leakage from discrete microaneurysms on fluorescein angiography) may be treated with focal laser photocoagulation, while diffuse macular edema (characterized by generalized macular edema on fluorescein angiography) may be treated with grid laser photocoagulation. Corticosteroids may reduce vascular permeability and inhibit VEGF production but are associated with serious adverse effects including cataracts and glaucoma with damage to the optic nerve. Corticosteroids can also worsen diabetes control. VEGF inhibitors (eg, ranibizumab, bevacizumab, pegaptanib), which reduce permeability and block the pathway leading to new blood vessel formation (angiogenesis) are being evaluated for the treatment of diabetic macular edema and proliferative diabetic retinopathy. For DME, outcomes of interest are macular thickness and visual acuity. For proliferative diabetic retinopathy, outcomes of interest are operative and perioperative outcomes and visual acuity.

Central and Branch Retinal Vein Occlusions

Retinal vein occlusions are classified by whether there is a CRVO or BRVO. CRVO is also categorized as ischemic or nonischemic. Ischemic CRVO is associated with a poor visual prognosis, with macular edema and permanent macular dysfunction occurring in virtually all patients. Nonischemic CRVO has a better visual prognosis, but many patients will have macular edema, and it may convert to the ischemic type within 3 years. Most of the vision loss associated with CRVO results from the main complications, macular edema and intraocular neovascularization. BRVO is a common retinal vascular disorder in adults between 60 and 70 years of age and occurs approximately 3 times more commonly than CRVOs. Macular edema is the most significant cause of central visual loss in BRVO.

Retinal vein occlusions are associated with increased venous and capillary pressure and diminished blood flow in the affected area, with a reduced supply of oxygen and nutrients. The increased pressure causes water flux into the tissue while the hypoxia stimulates the production of inflammatory mediators such as VEGF, which increases vessel permeability and induces new vessel growth. Intravitreal corticosteroid injections or implants have been used to treat the macular edema associated with retinal vein occlusions, with a modest beneficial effect on visual acuity. However, cataracts are a common adverse effect, and steroid-related pressure elevation occurs in about one third of patients, with some

requiring filtration surgery. Macular grid photocoagulation has also been used to improve vision in BRVO but is not recommended for CRVO. The serious adverse effects of available treatments have stimulated the evaluation of new treatments, including intravitreal injection of VEGF inhibitors. Outcomes of interest for retinal vein occlusions are macular thickness and visual acuity.

Retinopathy of Prematurity
ROP is a neovascular retinal disorder that primarily affects premature infants of low birth weight. It is one of the most common causes of childhood blindness in the United States. Typically, retinal vascularization begins at the optic nerve when the eye begins to develop (16 weeks of gestation) and reaches the edge of the retina at 40 weeks of gestation. If an infant is born prematurely, normal vessel growth may stop, followed by neovascularization at the interface between the vascular and avascular retinal areas. Stages of ROP are defined by vessel appearance and the level of retinal detachment, ranging from mild (stage 1) to severe (stage 5). Stage I or stage II ROP may resolve on its own. The optimal time for treatment is stage III, when a ridge with neovascularization extends into the vitreous gel. The neovascularization may progress and form fibrous scar tissue that causes partial (stage 4) or total retinal detachment (stage 5), accompanied by loss of vision. Both cryotherapy and laser therapy have been used to slow or reverse the abnormal growth of blood vessels in the peripheral areas of the retina. While successful in about 50% of cases, these treatments can cause myopia and permanent loss of the peripheral visual field. Vitrectomy may be needed when cryotherapy or laser therapy fail to induce regression.

Other
Other retinal vascular conditions that are being evaluated for treatment with VEGF inhibitors are cystoid macular edema resulting from vasculitis, Coats disease, Eales disease, idiopathic macular telangiectasia type II, neovascularization of the iris/neovascularization of the angle/neovascular glaucoma, pseudoxanthoma elasticum, radiation retinopathy, retinal neovascularization, rubeosis, Von Hippel-Lindau, and vitreous hemorrhage secondary to retinal neovascularization.

Summary
Angiogenesis inhibitors (eg, ranibizumab, bevacizumab, pegaptanib, aflibercept) can be given via intraocular injections as a treatment for disorders of retinal circulation. Ophthalmic disorders affecting the retinal circulation include proliferative diabetic retinopathy, diabetic macular edema, central (CRVO) or branch retinal vein occlusion (BRVO), and retinopathy of prematurity (ROP).

There is evidence that vascular endothelial growth factor (VEGF) inhibitors (bevacizumab, ranibizumab, aflibercept) are efficacious agents for the treatment of diabetic macular edema (DME) when given by the intravitreal route. A high-quality randomized controlled trial (RCT) with head-to-head comparison of aflibercept, bevacizumab, and ranibizumab was performed by the Diabetic Retinopathy Clinical Research Network (DRCRN). This trial demonstrated generally similar outcomes for the 3 agents, with some advantage of aflibercept in patients with worse visual acuity at baseline.

Additional evidence includes 2 sham-controlled trials and 3 trials that compared ranibizumab versus laser photocoagulation. These trials consistently show that ranibizumab is an efficacious agent for treating DME and results in superior outcomes compared with laser photocoagulation. Although for bevacizumab the quality of the other RCTs is less, and for aflibercept there are fewer trials completed, evidence from the DRCRN trial is sufficient to conclude that the these agents are at least as effective as ranibizumab for the treatment of DME. Evidence remains insufficient to determine if pegaptanib is as effective as alternative treatments.

For the treatment of proliferative diabetic retinopathy, evidence is available for ranibizumab, bevacizumab and pegaptanib. A single small RCT reported that pegaptanib was not significantly more effective than photocoagulation for patients with proliferative diabetic retinopathy. Analysis of data from the RISE and RIDE trials found that treatment with ranibizumab over 3 years led to improvement in proliferative diabetic retinopathy in a significantly greater proportion of eyes than those treated with sham injections for the first 2 years. In February 2015, the U.S. Food and Drug Administration (FDA) approved Lucentis™ to treat

diabetic retinopathy in patients with DME. A number of smaller RCTs report superior outcomes for bevacizumab as a single agent or as an adjunct to vitrectomy.

RCTs on the treatment of retinal vein occlusion are available for all 4 agents (ranibizumab, bevacizumab, pegaptanib, aflibercept). These trials are consistent in reporting that ranibizumab, bevacizumab, and aflibercept are efficacious agents in preserving visual acuity and reducing retinal thickness. The largest amount of evidence is available for ranibizumab and bevacizumab, but there is no evidence that either agent is superior to the others for this indication.

The evidence on the benefit of VEGF treatment for retinopathy of prematurity is limited. However, at least 2 RCTS, 1 high-quality trial using bevacizumab and a more problematic study using pegaptanib, report that recurrence of retinopathy is reduced compared with laser treatment alone. This evidence suggests that bevacizumab improves outcomes for infants with ROP when given by the intravitreal route.

Given the similarity in efficacy of aflibercept, bevacizumab, and ranibizumab, these 3 VEGF inhibitors may be considered medically necessary for the treatment of DME and proliferative retinopathy, retinal vein occlusion, and ROP. Based on clinical input, aflibercept, bevacizumab, and ranibizumab may be considered medically necessary for the treatment of neovascular glaucoma and rubeosis (neovascularization of the iris).

Trials with pegaptanib for diabetic macular edema and retinal vein occlusion do not conclusively demonstrate a gain in visual acuity with this treatment. Pegaptanib was reported to be superior to laser therapy in a large trial of infants with ROP, although this study did not describe the method of randomization or whether the treatment condition was masked. Therefore, intravitreal injection of pegaptanib for retinal vascular conditions is considered investigational.

Policy History

Date	Action
4/2016	New references added from BCBSA National medical policy.
8/2015	BCBSA National medical policy review. New medically necessary indications described. Ranibizumab, bevacizumab, and aflibercept considered equivalent and policy statements combined. Effective 8/1/2015.
2/2015	Clarified coding information.
5/2014	New references from BCBSA National medical policy.
6/2013	New references from BCBSA National medical policy.
2/04/2013	New policy describing coverage and non-coverage indications.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

1. Lucentis Prescribing Information. 2015; http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125156s106lbl.pdf. Accessed February 16, 2016.
2. Eylea Prescribing Information. 2014; http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125387s043lbl.pdf. Accessed February 16, 2016.

3. Ahmadieh H, Ramezani A, Shoeibi N, et al. Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial. Graefes Arch Clin Exp Ophthalmol. Apr 2008;246(4):483-489. PMID 17917738
4. O'Malley PG. Comparative effectiveness of anti-growth factor therapies for diabetic macular edema: summary of primary findings and conclusions. Arch Intern Med. Jul 9 2012;172(13):1014-1015. PMID 22688778
5. American Academy of Ophthalmology Retina Panel. Anti-vascular endothelial growth factor pharmacotherapy for diabetic macular edema: a report by the American Academy of Ophthalmology. Ophthalmology [Review]. 2012; 2012/08/25:2179-2188. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22917890. Accessed January 7, 2015.
6. Virgili G, Parravano M, Menchini F, et al. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for diabetic macular oedema. Cochrane Database Syst Rev. 2012;12:CD007419. PMID 23235642
7. Virgili G, Parravano M, Menchini F, et al. Anti-vascular endothelial growth factor for diabetic macular oedema. Cochrane Database Syst Rev. 2014;10:CD007419. PMID 25342124
8. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. Mar 26 2015;372(13):1193-1203. PMID 25692915
9. Massin P, Bandello F, Garweg JG, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes Care. Nov 2010;33(11):2399-2405. PMID 20980427
10. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. Apr 2012;119(4):789-801. PMID 22330964
11. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology. Oct 2013;120(10):20132022. PMID 23706949
12. Boyer DS, Nguyen QD, Brown DM, et al. Outcomes with As-Needed Ranibizumab after Initial Monthly Therapy: Long-Term Outcomes of the Phase III RIDE and RISE Trials. Ophthalmology. Dec 2015;122(12):2504-2513 e2501. PMID 26452713
13. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology. Apr 2011;118(4):615-625. PMID 21459215
14. Lang GE, Berta A, Eldem BM, et al. Two-year safety and efficacy of ranibizumab 0.5 mg in diabetic macular edema: interim analysis of the RESTORE extension study. Ophthalmology. Oct 2013;120(10):2004-2012. PMID 23725735
15. Schmidt-Erfurth U, Lang GE, Holz FG, et al. Three-Year Outcomes of Individualized Ranibizumab Treatment in Patients with Diabetic Macular Edema: The RESTORE Extension Study. Ophthalmology. Feb 1 2014. PMID 24491642
16. Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. Jun 2010;117(6):1064-1077 e1035. PMID 20427088
17. Elman MJ, Bressler NM, Qin H, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. Apr 2011;118(4):609-614. PMID 21459214
18. Nguyen QD, Shah SM, Heier JS, et al. Primary End Point (Six Months) Results of the Ranibizumab for Edema of the mAcula in diabetes (READ-2) study. Ophthalmology. Nov 2009;116(11):2175-2181 e2171. PMID 19700194
19. Nguyen QD, Shah SM, Khwaja AA, et al. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. Ophthalmology. Nov 2010;117(11):2146-2151. PMID 20855114
20. Do DV, Nguyen QD, Khwaja AA, et al. Ranibizumab for edema of the macula in diabetes study: 3-year outcomes and the need for prolonged frequent treatment. JAMA Ophthalmol. Feb 2013;131(2):139-145. PMID 23544200
21. Ishibashi T, Li X, Koh A, et al. The REVEAL Study: Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy in Asian Patients with Diabetic Macular Edema. Ophthalmology. Jul 2015;122(7):1402-1415. PMID 25983216
22. Berger A, Sheidow T, Cruess AF, et al. Efficacy/safety of ranibizumab monotherapy or with laser versus laser monotherapy in DME. Can J Ophthalmol. Jun 2015;50(3):209-216. PMID 26040221

23. Soheilian M, Ramezani A, Obudi A, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. Ophthalmology. Jun 2009;116(6):1142-1150. PMID 19376585
24. Soheilian M, Garfami KH, Ramezani A, et al. Two-year results of a randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus laser in diabetic macular edema. Retina. Feb 2012;32(2):314-321. PMID 22234244
25. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. Ophthalmology. Jun 2010;117(6):1078-1086 e1072. PMID 20416952
26. Do DV, Schmidt-Erfurth U, Gonzalez VH, et al. The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. Ophthalmology. Sep 2011;118(9):1819-1826. PMID 21546089
27. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. Ophthalmology. Oct 2015;122(10):2044-2052. PMID 26198808
28. Cunningham ET, Jr., Adamis AP, Altaweel M, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology. Oct 2005;112(10):1747-1757. PMID 16154196
29. Sultan MB, Zhou D, Loftus J, et al. A Phase 2/3, Multicenter, Randomized, Double-Masked, 2-Year Trial of Pegaptanib Sodium for the Treatment of Diabetic Macular Edema. Ophthalmology. Apr 27 2011. PMID 21529957
30. Simunovic MP, Maberley DA. Anti-vascular endothelial growth factor therapy for proliferative diabetic retinopathy: A Systematic Review and Meta-Analysis. Retina. Oct 2015;35(10):1931-1942. PMID 26398553
31. Gross JG, Glassman AR, Jampol LM, et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA. Nov 24 2015;314(20):2137-2146. PMID 26565927
32. Diabetic Retinopathy Clinical Research Network. Randomized clinical trial evaluating intravitreal ranibizumab or saline for vitreous hemorrhage from proliferative diabetic retinopathy. JAMA Ophthalmol. Mar 2013;131(3):283293. PMID 23370902
33. Ip MS, Domalpally A, Sun JK, et al. Long-term Effects of Therapy with Ranibizumab on Diabetic Retinopathy Severity and Baseline Risk Factors for Worsening Retinopathy. Ophthalmology. Feb 2015;122(2):367-374. PMID 25439595
34. Javanovic S, Canadanovic V, Sabo A, et al. Intravitreal bevacizumab injection alone or combined with macular photocoagulation compared to macular photocoagulation as primary treatment of diabetic macular edema. Vojnosanit Pregl. Oct 2015;72(10):876-882. PMID 26665553
35. Cho WB, Moon JW, Kim HC. Intravitreal triamcinolone and bevacizumab as adjunctive treatments to panretinal photocoagulation in diabetic retinopathy. Br J Ophthalmol. Jul 2010;94(7):858-863. PMID 20606024
36. Mirshahi A, Roohipoor R, Lashay A, et al. Bevacizumab-augmented retinal laser photocoagulation in proliferative diabetic retinopathy: a randomized double-masked clinical trial. Eur J Ophthalmol. Mar-Apr 2008;18(2):263-269. PMID 18320520
37. Smith JM, Steel DH. Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy. Cochrane Database Syst Rev. 2011;5:CD008214. PMID 21563165
38. Ahmadieh H, Shoeibi N, Entezari M, et al. Intravitreal bevacizumab for prevention of early postvitrectomy hemorrhage in diabetic patients: a randomized clinical trial. Ophthalmology. Oct 2009;116(10):1943-1948. PMID 19699531
39. Hernandez-Da Mota SE, Nunez-Solorio SM. Experience with intravitreal bevacizumab as a preoperative adjunct in 23-G vitrectomy for advanced proliferative diabetic retinopathy. Eur J Ophthalmol. Nov-Dec 2010;20(6):10471052. PMID 20491044
40. di Lauro R, De Ruggiero P, di Lauro MT, et al. Intravitreal bevacizumab for surgical treatment of severe proliferative diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. Jun 2010;248(6):785-791. PMID 20135139
41. Gonzalez VH, Giuliari GP, Banda RM, et al. Intravitreal injection of pegaptanib sodium for proliferative diabetic retinopathy. Br J Ophthalmol. Nov 2009;93(11):1474-1478. PMID 19692371
42. Yeh S, Kim SJ, Ho AC, et al. Therapies for macular edema associated with central retinal vein occlusion: a report by the American Academy of Ophthalmology. Ophthalmology. Apr 2015;122(4):769-778. PMID 25576994

43. Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. Jun 2010;117(6):1124-1133 e1121. PMID 20381871
44. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology. Oct 2011;118(10):2041-2049. PMID 21715011
45. Holz FG, Roider J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. Br J Ophthalmol. Mar 2013;97(3):278-284. PMID 23298885
46. Korobelnik JF, Holz FG, Roider J, et al. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. Ophthalmology. Jan 2014;121(1):202-208. PMID 24084497
47. Ogura Y, Roider J, Korobelnik JF, et al. Intravitreal aflibercept for macular edema secondary to central retinal vein occlusion: 18-month results of the phase 3 GALILEO study. Am J Ophthalmol. Nov 2014;158(5):1032-1038. PMID 25068637
48. Heier JS, Clark WL, Boyer DS, et al. Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion: two-year results from the COPERNICUS study. Ophthalmology. Jul 2014;121(7):1414-1420 e1411. PMID 24679444
49. Epstein DL, Algvere PV, von Wendt G, et al. Bevacizumab for macular edema in central retinal vein occlusion: a prospective, randomized, double-masked clinical study. Ophthalmology. Jun 2012;119(6):1184-1189. PMID 22424833
50. Mitry D, Bunce C, Charteris D. Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. Cochrane Database Syst Rev. 2013;1:CD009510. PMID 23440840
51. Campochiaro PA, Heier JS, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. Jun 2010;117(6):1102-1112 e1101. PMID 20398941
52. Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained Benefits from Ranibizumab for Macular Edema Following Branch Retinal Vein Occlusion: 12-Month Outcomes of a Phase III Study. Ophthalmology. Aug 2011;118(8):1594-1602. PMID 21684606
53. Moradian S, Faghihi H, Sadeghi B, et al. Intravitreal bevacizumab vs. sham treatment in acute branch retinal vein occlusion with macular edema: results at 3 months (Report 1). Graefes Arch Clin Exp Ophthalmol. Feb 2011;249(2):193-200. PMID 21337043
54. Varma R, Bressler NM, Suner I, et al. Improved Vision-Related Function after Ranibizumab for Macular Edema after Retinal Vein Occlusion: Results from the BRAVO and CRUISE Trials. Ophthalmology. Oct 2012;119(10):2108-2118. PMID 22817833
55. Epstein DL, Algvere PV, von Wendt G, et al. Benefit from Bevacizumab for Macular Edema in Central Retinal Vein Occlusion: Twelve-Month Results of a Prospective, Randomized Study. Ophthalmology. Aug 16 2012. PMID 22902212
56. Cekic O, Cakir M, Yazici AT, et al. A comparison of three different intravitreal treatment modalities of macular edema due to branch retinal vein occlusion. Curr Eye Res. Oct 2010;35(10):925-929. PMID 20858114
57. Narayanan R, Panchal B, Das T, et al. A randomised, double-masked, controlled study of the efficacy and safety of intravitreal bevacizumab versus ranibizumab in the treatment of macular oedema due to branch retinal vein occlusion: MARVEL Report No. 1. Br J Ophthalmol. Jul 2015;99(7):954-959. PMID 25631483
58. Rajagopal R, Shah GK, Blinder KJ, et al. Bevacizumab Versus Ranibizumab in the Treatment of Macular Edema Due to Retinal Vein Occlusion: 6-Month Results of the CRAVE Study. Ophthalmic Surg Lasers Imaging Retina. Sep 2015;46(8):844-850. PMID 26431300
59. Campochiaro PA, Clark WL, Boyer DS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study. Ophthalmology. Mar 2015;122(3):538-544. PMID 25315663
60. Wroblewski JJ, Wells JA, 3rd, Adamis AP, et al. Pegaptanib sodium for macular edema secondary to central retinal vein occlusion. Arch Ophthalmol. Apr 2009;127(4):374-380. PMID 19365011
61. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. Feb 17 2011;364(7):603-615. PMID 21323540
62. Autrata R, Krejcirova I, Senkova K, et al. Intravitreal pegaptanib combined with diode laser therapy for stage 3+ retinopathy of prematurity in zone I and posterior zone II. Eur J Ophthalmol. Sep-Oct 2012;22(5):687-694. PMID 22669848
63. Simha A, Braganza A, Abraham L, et al. Anti-vascular endothelial growth factor for neovascular glaucoma. Cochrane Database Syst Rev. 2013;10:CD007920. PMID 24089293

64. American Academy of Ophthalmology Retina/Vitreous Panel. Diabetic Retinopathy Preferred Practice Pattern. 2016; http://www.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp-updated-2016. Accessed February 25, 2016.
65. American Academy of Ophthalmology Retina/Vitreous Panel. Retinal Vein Occlusions Preferred Practice Pattern Guidelines. 2015; http://www.aaojournal.org/content/preferred-practice-pattern. Accessed February 25, 2016.
66. National Institute for Health and Clinical Excellence (NICE). Final appraisal determination: Ranibizumab for the treatment of diabetic macular oedema TA274. 2013; http://www.nice.org.uk/guidance/TA274. Accessed January 7, 2015.
67. National Institute for Health and Clinical Excellence (NICE). TA 274 Ranibizumab for treating diabetic macular oedema. 2013; http://publications.nice.org.uk/ranibizumab-for-treating-diabetic-macular-oedema-rapid-review-of-technology-appraisal-guidance-ta274/about-this-guidance. Accessed January 7, 2015.
68. National Institute for Health and Clinical Excellence (NICE). TA 283 Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion. 2013; http://publications.nice.org.uk/ranibizumab-for-treating-visual-impairment-caused-by-macular-oedema-secondary-to-retinal-vein-ta283. Accessed January 7, 2015.