



MASSACHUSETTS

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Medical Policy

Intravitreal Angiogenesis Inhibitors for Retinal Vascular Conditions

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NCD/LCD: NA

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Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM 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 BlueSM	No
Medicare PPO BlueSM	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 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](#)

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