Drug and Biologic Coverage Policy

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Coverage Policy Number 1206

Vascular Endothelial Growth Factor (VEGF) Inhibitors for Ocular Use

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Vascular Endothelial Growth Factor (VEGF) Inhibitors for Ocular Use includes the following products:

- **aflibercept** for intravitreal injection **(Eylea™)**
- **pegaptanib sodium** for intravitreal injection **(Macugen®)**
- **ranibizumab** for intravitreal injection **(Lucentis®)**

Aflibercept for intravitreal injection (Eylea™) is considered medically necessary for the treatment of ONE of the following:

- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)
- Macular Edema following retinal vein occlusion (RVO)
- Neovascular (wet) Age-Related Macular Degeneration

Pegaptanib sodium for intravitreal injection (Macugen®) is considered medically necessary when ALL the following criteria are met:

- For the treatment of neovascular (wet) age-related macular degeneration (AMD)

Ranibizumab for intravitreal injection (Lucentis®) is considered medically necessary for the treatment of ONE of the following:

- Choroidal Neovascularization secondary to angioid streaks (AS) or pseudoxanthoma elasticum (PXE)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)
- Macular Edema following Retinal Vein Occlusion (RVO)
- Neovascular (wet) Age-Related Macular Degeneration (AMD)
- Myopic Choroidal Neovascularization (mCNV)
- Ocular Histoplasmosis Syndrome

Initial authorization is up to 12 months.

Vascular Endothelial Growth Factor (VEGF) Inhibitors for Ocular Use are considered medically necessary for continued use when the following are met:

- Individual continues to meet the initial criteria
- Attestation of beneficial clinical response

Reauthorization for up to 12 months

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Vascular Endothelial Growth Factor (VEGF) Inhibitors for Ocular Use are considered experimental, investigational or unproven for ANY other use including the following:

- Best disease
- Coats' disease
- central serous chorioretinopathy
- radiation maculopathy
- refractory noninfectious uveitic cystoid macular edema
- uveitis with childhood neovascularization

The concomitant use of greater than one VEGF Inhibitor in the same eye is not covered as it is considered experimental, investigational or unproven.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indications

FDA Approved Indication

Brand Name	Approved Indication
Eylea	Eylea is indicated for the treatment of patients with: • Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)
Lucentis	Lucentis is indicated for the treatment of patients with: • Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)

Brand Name	Approved Indication
	• Myopic Choroidal Neovascularization (mCNV)
Macugen	Macugen is indicated for the treatment of neovascular (wet) age-related macular degeneration.

Recommended Dosing

FDA Recommended Dosing

Brand Name	Recommended Dosing
Eylea	**Neovascular (Wet) Age-Related Macular Degeneration (AMD)** The recommended dose for Eylea is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although Eylea may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when Eylea was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly. **Macular Edema Following Central Retinal Vein Occlusion (CRVO)** The recommended dose for Eylea is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly) **Diabetic Macular Edema (DME)** The recommended dose for Eylea is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although Eylea may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when Eylea was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months). **Diabetic Retinopathy (DR)** The recommended dose for Eylea is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although Eylea may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when Eylea was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).
Lucentis	**Neovascular (Wet) Age-Related Macular Degeneration (AMD)** Lucentis 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days). Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment. In the 9 months after three initial monthly doses, less frequent dosing with 4-5 doses on average is expected to maintain visual acuity while monthly dosing may be expected to result in an additional average 1-2 letter gain. Patients should be assessed regularly. Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Compared with continued monthly dosing, dosing every 3 months over the next 9 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average. Patients should be assessed regularly. **Macular Edema Following Retinal Vein Occlusion (RVO)**

Brand Name	Recommended Dosing
	Lucentis 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days). In Studies RVO-1 and RVO-2, patients received monthly injections of Lucentis for six months. In spite of being guided by optical coherence tomography and visual acuity re-treatment criteria, patients who were then not treated at Month 6 experienced on average, a loss of visual acuity at Month 7, whereas patients who were treated at Month 6 did not. **Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR):** Lucentis 0.3 mg (0.05 mL of 6mg/ ml solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days). **Myopic Choroidal Neovascularization (mCNV)** Lucentis 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be initially administered by intravitreal injection once a month (approximately 28 days) for up to 3 months. Patients may be retreated if needed.
Macugen	Macugen 0.3 mg should be administered once every six weeks by intravitreous injection into the eye to be treated.

Drug Availability

Brand Name	Drug Availability
Eylea	Single-use vial designed to provide 0.05 mL of 40 mg/mL solution for intravitreal injection.
Lucentis	Single-use, 2-mL glass vial designed to provide 0.05 mL for intravitreal injection: • 6 mg/mL solution • 10 mg/mL solution Single-use prefilled syringe designed to provide 0.05 mL for intravitreal injections: • 10 mg/mL solution
Macugen	Single-use glass syringe pre-filled with 0.3 mg of Macugen in a nominal 90 µL solution for intravitreal injection.

General Background

Pharmacology

EYLEA

Aflibercept is a soluble decoy receptor, binding PlGF and all isoforms of VEGF-A with high affinity. Aflibercept interferes with the activation of the VEGF receptors, thereby preventing the cascade of events leading to neovascularization and vascular leakage.

LUCENTIS

Ranibizumab binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, VEGF. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion, and is thought to contribute to the progression of neovascular AMD and macular edema following RVO. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

MACUGEN

Pegaptanib is a synthetic oligonucleotide apatmer with high affinity for VEGF. It delays choroidal neovascularization by binding VEGF, preventing it from binding to its receptor present on vascular endothelial cells of the subretinal choroid.

Professional Societies/Organizations

American Academy of Ophthalmology (AAO)

The current preferred practice patterns published by the AAO indicate that anti-VEGF medications are first- line treatment options to treat and stabilize the majority of neovascular age-related macular degeneration (AMD) cases. The committee states that anti-VEGF therapy is usually well tolerated with few serious adverse events, such as infectious endophthalitis or retinal detachment. If either of these adverse events is suspected, a timely evaluation is warranted. (AAO, 2015)

In 2015, citing a positive risk to benefit ratio associated with anti-VEGF treatment, the AAO preferred practice pattern regarding retinal vein occlusion states these medications should be the initial treatment for macular edema related to BRVO. The AAO further mentions several trials that have shown the efficacy of the anti-VEGFs in CRVO related macular edema, but does not call out the anti-VEGFs as initial therapy in this situation. The organization describes this class of medications as the safest treatments for macular edema associated with BRVO and CRVO. (AAO, 2015)

The 2016 update of the AAO guidelines for diabetic retinopathy state that intravitreal anti-VEGF therapy is recommended as first line treatment for center involving macular edema, followed by laser treatment as necessary. In addition, the organization remarks that intravitreal anti-VEGF therapy is an alternative treatment in individuals with high-risk proliferative diabetic retinopathy without macular edema, citing data from one trial assessing the non-inferiority of intravitreous ranibizumab compared to panretinal photocoagulation for visual acuity outcomes in individuals with proliferative diabetic retinopathy. (AAO, 2016)

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

No recommendations are available for Vascular Endothelial Growth Factor (VEGF) inhibitors.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)

There are no CMS National Coverage Determinations for Eylea, Lucentis or Macugen.

Clinical Efficacy

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

Visual improvement was similar between bevacizumab and ranibizumab, and between aflibercept and ranibizumab in patients with neovascular AMD. Mean best corrected visual acuity (BCVA) letters increased from baseline for aflibercept (+6.6 to +10.9), bevacizumab (+7.4 to +8.5), and ranibizumab (+7.9 to +9.4), but decreased for pegaptanib (−7.3). Mean foveal thickness decreased from baseline for aflibercept (−116 to −157 micron), bevacizumab (−62 to −112 micron) and ranibizumab (−116 to −139 micron). Foveal thickness may decrease more with ranibizumab than bevacizumab. Foveal thickness reductions with pegaptanib were not addressed in any direct comparative trials. (Berg, 2015; Heier, 2012; Schmid-Kubista, 2011; Schmidt-Erfurth, 2014: Scholler, 2014; Solomon, 2014; Yuzawa, 2015)

Diabetic Macular Edema (DME)

Intravitreal bevacizumab or ranibizumab cause similar improvements in BCVA from baseline, while foveal thickness may decrease more with ranibizumab than bevacizumab. Intravitreal aflibercept may cause greater improvement in BCVA and foveal thickness than bevacizumab or ranibizumab, especially in patients with baseline BCVA worse than 20/50. In a meta-analysis that evaluated indirect comparisons, BCVA improved significantly less with pegaptanib than aflibercept, bevacizumab, or ranibizumab; foveal thickness was not reported. Mean BCVA letters increased from baseline for aflibercept (+13.3), bevacizumab (+2.5 to +9.7), pegaptanib (+5.1, based on pooled data), and ranibizumab (+3 to +11.2). Foveal thickness decreased for aflibercept (−169 micron), bevacizumab (−101 to −141.5 micron), and ranibizumab (−136 to −150.5 micron). (Ekinci, 2014; Nepomuceno, 2013; Ollendorf, 2013; Wells, 2015)

Other Covered Use

Choroidal Neovascularization (CNV) secondary to angioid streaks (AS) or pseudoxanthoma elasticum (PXE)

Treatment with anti-vascular endothelial growth factor (VEGF) such as ranibizumab has demonstrated efficacy in the treatment of choroidal neovascularization (CNV) secondary to angioid streaks (AS) in small studies with a

short follow-up duration. (Shah, 2012; Vadala, 2010) A long-term retrospective study reinforced the short-term outcomes. (Tilleul, 2016) All of these studies were in patients with angioid streaks-associated CNV in causes other than pseudoxanthoma elasticum (PXE).

In angioid streaks-associated choroidal neovascularization (CNV) secondary to pseudoxanthoma elasticum (PXE) specifically, positive visual outcomes over a long term with anti-VEGF therapy has been reported in few case reports and smaller studies (Finger, 2011; Myung, 2010; Yilmaz, 2014; Zebardast, 2012)

In France, ranibizumab was granted temporary reimbursement from October 2011 to October 2014, for the treatment of patients with choroidal neovascularization secondary to pseudoxanthoma elasticum. The PIXEL study was conducted to evaluate the long-term effectiveness and safety of ranibizumab 0.5 mg in 72 patients (98 eyes) with CNV secondary to PXE. The main objective was to assess changes in best-corrected visual acuity over time. The mean visual acuity (VA) was 64.6 letters at the first ranibizumab injection, which was maintained at the 1-year follow-up (64.7 letters). VA remained stable until the 4-year follow-up. (Mimoun, 2017)

Ocular Histoplasmosis Syndrome (OHS)
The effect of ranibizumab on choroidal neovascularization, secondary to causes other than age-related macular degeneration, was studied in a randomized, controlled trial, and included 9 patients with ocular histoplasmosis syndrome. Thirty patients were randomized to either monthly intravitreal ranibuzimab or 3 monthly intravitreal injections followed by PRN injections of ranibizumab. Results revealed no difference between the groups in visual acuity or central retinal thickness. In addition, a retrospective chart review of 52 patients treated with either bevacizumab or ranibizumab showed significant improvement in visual acuity from baseline in patients with choroidal neovascularization secondary to OHS. (Heier, 2011; Nielsen, 2012)

Safety Profile

Ocular
Endophthalmitis risk may be higher with bevacizumab than pegaptanib or ranibizumab, and appears similar between aflibercept, pegaptanib, and ranibizumab. Risk of other ocular adverse events appears similar between bevacizumab and ranibizumab. Comparative data for other ocular adverse events are not available for aflibercept and pegaptanib.

Systemic
Risk of hemorrhage, myocardial infarction, and arterial thrombosis appears similar with bevacizumab, pegaptanib, and ranibizumab. All-cause mortality and stroke may be slightly more common with bevacizumab and ranibizumab based on observational data and secondary analyses, although a Cochrane systematic review found no difference between these agents. Compared with bevacizumab and ranibizumab, risk of stroke is similar with pegaptanib, but all-cause mortality may be higher with pegaptanib. Gastrointestinal adverse events and dermatologic adverse events may be more common with bevacizumab than ranibizumab. No comparative data are available for systemic adverse events with aflibercept.
(Berg, 2015;Casparis, 2014; Curtis, 2010;Eckinci 2014; Heier, 2012;Inoue, 2011; Johnson, 2014;Moja, 2014; Nepomuceno, 2013;Schmid-Kubista, 2011;Schmidt-Erfurth, 2014;Scholler, 2014;Soloman, 2014; Wells, 2015; Yuzawa 2015)

Off Label Uses

AHFS Drug Information 2019 Edition does not support any off-label uses of Eylea, Lucentis or Macugen.

Experimental, Investigational, Unproven Uses

Macugen has been studied for use in diabetic macular edema, however, there is insufficient published data in terms of safety and efficacy to support its use for this indication. (Ollendorf, 2013)

There is insufficient evidence in the peer-reviewed published scientific literature to support the safety and efficacy of the VEGF inhibitors in Best disease (Chaudhary, 2013), Coats' disease (Chaudhary, 2013), central serous chorioretinopathy (Salehi, 2015), radiation maculopathy (Seibel, 2016), refractory noninfectious uveitic cystoid macular edema (Lasave, 2009) and uveitis with childhood neovascularization (Chaudhary, 2013).

In addition, there are no published, randomized controlled trials evaluating the efficacy and safety of the concurrent use of intravitreal VEGF inhibitors.

Coding/ Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered when medically necessary:

HCPCS Codes	Description
J0178	Injection, aflibercept, 1 mg
J2503	Injection, pegaptanib sodium, 0.3 mg
J2778	Injection, ranibizumab, 0.1 mg

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