Subject  Vascular Endothelial Growth Factor (VEGF) Inhibitors for Ocular Use

Effective Date............................. 1/15/2018
Next Review Date ...................... 1/15/2019
Coverage Policy Number...............1206

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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®)

Cigna covers pegaptanib sodium for intravitreal injection (Macugen®) as medically necessary for the treatment of neovascular (wet) age-related macular degeneration (AMD).

Cigna covers aflibercept for intravitreal injection (Eylea™) as medically necessary for ANY of the following indications:
- diabetic macular edema (DME)
- diabetic retinopathy (DR) in patients with DME
- macular edema following retinal vein occlusion (RVO)
- neovascular (wet) age-related macular degeneration

Cigna covers ranibizumab for intravitreal injection (Lucentis®) as medically necessary for ANY of the following indications:
- 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

Cigna does not cover the use of Vascular Endothelial Growth Factor (VEGF) Inhibitors for Ocular Use for any other indication because it is considered experimental, investigational or unproven.

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

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Vascular Endothelial Growth Factor (VEGF) Inhibitors for Ocular Use.

### FDA Approved Indication

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Approved Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eylea</td>
<td>Eylea is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD), diabetic macular edema (DME), diabetic retinopathy (DR) in patients with DME and macular edema following retinal vein occlusion (RVO).</td>
</tr>
<tr>
<td>Lucentis</td>
<td>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, proliferative diabetic retinopathy (PDR) in patients with diabetic macular edema (DME)</td>
</tr>
<tr>
<td>Macugen</td>
<td>Macugen is indicated for the treatment of neovascular (wet) age-related macular degeneration.</td>
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</table>

### FDA Recommended Dosing

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Recommended Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eylea</td>
<td><strong>Neovascular (Wet) Age-Related Macular Degeneration (AMD)</strong>&lt;br&gt;The recommended dose for Eylea is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (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 (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).  &lt;br&gt;<strong>Macular Edema Following Central Retinal Vein Occlusion (CRVO)</strong>&lt;br&gt;The recommended dose for Eylea is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly)  &lt;br&gt;<strong>Diabetic Macular Edema (DME)</strong>&lt;br&gt;The recommended dose for Eylea is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (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 (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).</td>
</tr>
<tr>
<td>Lucentis</td>
<td></td>
</tr>
<tr>
<td>Macugen</td>
<td></td>
</tr>
</tbody>
</table>
### Diabetic Retinopathy (DR) in Patients with DME
The recommended dose for Eylea is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (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 (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 less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible. Compared to continual monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months.

**Macular Edema Following Retinal Vein Occlusion (RVO)**
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

### Macugen
Macugen 0.3 mg should be administered once every six weeks by intravitreous injection into the eye to be treated.

### Drug Availability

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug Availability</th>
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<tbody>
<tr>
<td><strong>Eylea</strong></td>
<td>Single-use vial designed to provide 0.05 mL of 40 mg/mL solution for intravitreal injection.</td>
</tr>
<tr>
<td><strong>Lucentis</strong></td>
<td>Single-use, 2-mL glass vial with a blue cap designed to deliver 0.05 mL of 10 mg/mL ranibizumab solution. Single-use, 2-mL glass vial with a white cap designed to deliver 0.05 mL of 6 mg/mL ranibizumab solution</td>
</tr>
<tr>
<td><strong>Macugen</strong></td>
<td>Single-use glass syringe pre-filled with 0.3 mg of Macugen in a nominal 90 μL deliverable volume pack.</td>
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</table>

### General Background

**Guidelines**
**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 endophthalmitis or retinal detachment. If either of these adverse events is suspected, a timely evaluation is warranted.

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 most safe treatments for macular edema associated with BRVO and CRVO.

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. (Gross, 2015)

**EYLEA**

**Pharmacology**
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**

**Pharmacology**
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.

**Other Covered Use**

**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)

**MACUGEN**

**Pharmacology**
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.

**VEGF Comparative Clinical Efficacy and Safety**

**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

**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)

**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; Solomon, 2014; Wells, 2015; Yuzawa 2015)

**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, Coats' disease, central serous chorioretinopathy, radiation maculopathy, refractory noninfectious uveitic cystoid macular edema and uveitis with childhood neovascularization. (Peiretti, 2017; Seibel, 2016; Salehi, 2015; Chaudhary, 2013; Lasave, 2009)

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:**

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>C9257**</td>
<td>Injection, bevacizumab, 0.25 mg</td>
</tr>
<tr>
<td>J0178</td>
<td>Injection, aflibercept, 1 mg</td>
</tr>
</tbody>
</table>
**when covered by medical benefit, pre-certification is not required**

### References


19. Lasave AF, Zeballos DG, El-Haig WM, et al. Short-term results of a single intravitreal bevacizumab (Avastin) injection versus a single intravitreal triamcinolone acetonide (Kenacort) injection for the...