Vascular Endothelial Growth Factor (VEGF) Inhibitors
Ocular Use
Drug Class Monograph
(Medical Benefit)

Line of Business: Medi-Cal
Effective Date: May 17, 2017
Revision Date: May 17, 2017

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutic Subcommittee.

Drugs: Avastin (bevacizumab), Eylea (aflibercept), Lucentis (ranibizumab), Macugen (pegaptanib sodium)

Policy/Criteria:

A. Avastin (bevacizumab)

Diagnosis:
  a. Age related macular degeneration
  OR
  b. Macular edema with retinal vein occlusion
  OR
  c. Choroidal retinal neovascularization
  OR
  d. Diabetic macular edema
  OR
  e. Diabetic retinopathy

Specialist: Ophthalmologist
B. **Lucentis** (ranibizumab)

**Diagnosis:**
- a. Neovascular (Wet) Age-Related Macular Degeneration
- OR
- b. Macular Edema following Retinal Vein Occlusion (RVO)
- OR
- c. Diabetic Macular Edema (DME)
- OR
- d. Diabetic retinopathy
- OR
- e. Myopic choroidal neovascularization

**Specialist:** Ophthalmologist

C. **Eylea** (aflibercept)

**Diagnosis:**
- a. Neovascular (Wet) Age-Related Macular Degeneration
- OR
- b. Macular Edema following Retinal Vein Occlusion (RVO)
- OR
- c. Diabetic Macular Edema (DME)
- OR
- d. Diabetic retinopathy

**Specialist:** Ophthalmologist

D. **Macugen** (pegaptanib sodium)

**Diagnosis:**
- a. Neovascular (Wet) Age-Related Macular Degeneration

**Specialist:** Ophthalmologist
Clinical Justification:

Local Coverage Article: Intraocular Bevacizumab Coding/Billing Guideline (A53008)

- Bevacizumab is not currently packaged and prepared by the manufacturer in doses appropriate for intravitreal injection. Physicians routinely obtain single doses prepared by qualified compounding pharmacies to minimize risk of contamination of the injected drug.
- Consistent with the statement of April 2006 of the American Academy of Ophthalmology (AAO) in support of this use of Bevacizumab, physicians should provide appropriate informed consent with respect to the off-label use of this drug and maintain it in the patient chart.
- Current scientific literature published in the peer-reviewed core medical journals supports these uses of this drug. The published experience shows that patients with wet macular degeneration may require regular injections for up to a year if new vessels appear and many may require injections even longer. The most recent clinical trial data now extends out beyond five years and demonstrates that most patients continue to require treatment beyond two years.

<table>
<thead>
<tr>
<th>Non-FDA approved indications for Bevacizumab</th>
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<tbody>
<tr>
<td>Neovascular age related macular degeneration (AMD)</td>
</tr>
<tr>
<td>Macular edema following retinal vein occlusion</td>
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<tr>
<td>Diabetic macular edema</td>
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<tr>
<td>Retinal vascular occlusion</td>
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<tr>
<td>Cystoids macular degeneration</td>
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<tr>
<td>Diabetic retinopathy</td>
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<tr>
<td>Proliferative retinopathy</td>
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<tr>
<td>Glaucoma with vascular disorders</td>
</tr>
<tr>
<td>Retinal neovascularization with associated conditions</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
</tr>
</tbody>
</table>
1. Recommended treatment for age-related macular degeneration with macular choroidal neovascularization
   a. Aflibercept intravitreal 2.0 mg
      - Dosed every 4 weeks and every 8 weeks after three monthly loading doses
      - Noninferior efficacy to 0.5 mg ranibizumab dosed every 4 weeks.
      - Every 8-week maintenance treatment regimen has been shown to have comparable results to every 4 weeks in the first year of therapy
   b. Bevacizumab intravitreal 1.25 mg
      - Improvements in visual acuity and decreased retinal thickness by optical coherence tomography (OCT) following treatment.
      - Informed consent for patients with respect to the off-label use.
   c. Ranibizumab intravitreal 0.5 mg
      - Ranibizumab PRN had noninferior visual acuity improvements compared with monthly injections.
      - There does not appear to be a significant difference in efficacy between ranibizumab and bevacizumab.

2. For VEGF inhibitor intravitreal treatments, the following are noted:
   a. Demonstrated improved visual and anatomic outcomes
   b. Considered first-line therapy for most cases of neovascular AMD
   c. Generally well tolerated and rarely associated with serious adverse events such as infectious endophthalmitis or retinal detachment
   d. There are theoretical risks for systemic arterial thromboembolic events and increased intraocular pressure
   e. Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, retinal detachment, or decreased vision, and they should be re-examined promptly
   f. Monitoring of monocular near vision
   g. Examine at regular intervals by means of biomicroscopy of the fundus
   h. Optical coherence tomography, fluorescein angiography, and fundus photography may be used to detect signs of active exudation or disease progression
   i. A history and examination are recommended at follow-up visits
   j. Return exam 4 weeks after treatment; subsequent follow-up depends on the clinical findings

3. Pegaptanib sodium treatment does not improve visual acuity on average in patients with new-onset neovascular AMD and is rarely used in current clinical practice
<table>
<thead>
<tr>
<th>MOA</th>
<th>Avastin (bevacizumab)</th>
<th>Eylea (aflibercept)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Binds VEGF and prevents its interaction to its receptors (Flt-1 and KDR) on endothelial cells</td>
<td>Binds VEGF-A and PGF to inhibit the activation of VEGFR-1 and VEGFR-2 receptors</td>
</tr>
<tr>
<td>Usual Dosing</td>
<td>1.25 mg monthly for 3 months, then given monthly or as needed</td>
<td>2 mg monthly for the first 3 months, then 2 mg once every 2 months</td>
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<tr>
<td>Administration</td>
<td></td>
<td>Intravitreal injection</td>
</tr>
<tr>
<td>Dosage adjustment in renal impairment</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>PK/PD</td>
<td>Distribution: 46 ml/kg</td>
<td>Absorption: Levels undetectable after 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Protein binding: ~97%</td>
<td>Distribution: ~6 L</td>
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<tr>
<td></td>
<td>Metabolism: Reticuloendothelial system</td>
<td>Metabolism: Proteolysis</td>
</tr>
<tr>
<td></td>
<td>Half-life elimination: 5-10 days</td>
<td>Half-life elimination: 5-6 days</td>
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<tr>
<td></td>
<td>Time to peak, plasma: ~8 days</td>
<td>Time to peak, plasma: 1-3 days</td>
</tr>
<tr>
<td></td>
<td>Excretion: Reticuloendothelial system</td>
<td>Excretion: Target mediated disposition via binding to free endogenous VEGF</td>
</tr>
<tr>
<td>Drug-drug interaction</td>
<td>paclitaxel/carboplatin</td>
<td>No</td>
</tr>
<tr>
<td>Common Side effects</td>
<td>Epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, exfoliative dermatitis</td>
<td>Conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, vitreous detachment</td>
</tr>
<tr>
<td>Serious allergic and hypersensitivity</td>
<td>No</td>
<td>Yes; Anaphylaxis, rash, Hypersensitivity reaction</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Advise pregnant women of potential risk to fetus.</td>
<td>Category C; should be used during pregnancy only if the benefits outweigh the risks</td>
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<tr>
<td>Lactation</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Storage and stability</td>
<td>Store at 2–8°C (36–46°F)</td>
<td></td>
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<tr>
<td>How supplied</td>
<td>100 mg or 400 mg vials</td>
<td>1 single-use, 3-mL glass vial with 0.05 mL of 40 mg/mL aflibercept</td>
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<tr>
<th>MOA</th>
<th>Lucentis (ranibizumab)</th>
<th>Macugen (pegaptanib sodium)</th>
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<td></td>
<td>Binds and inhibits the biologic activity of all isoforms of human VEGF-A</td>
<td>Selective VEGF antagonist that binds to the 165 isoform of VEGF-A</td>
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<tr>
<td>Usual Dosing</td>
<td>0.5 mg monthly</td>
<td>0.3 mg once every six weeks</td>
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<td>Administration</td>
<td>Intravitreal injection</td>
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<tr>
<td>Dosage adjustment in renal impairment</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>PK/PD</td>
<td>Absorption: Slow</td>
<td>Absorption: Slow</td>
</tr>
<tr>
<td></td>
<td>Distribution: ~8.91 ml</td>
<td>Metabolism: Metabolized by endo- and exonucleases</td>
</tr>
<tr>
<td></td>
<td>Metabolism: Not extensively metabolized</td>
<td>Bioavailability: 70-100%</td>
</tr>
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</table>
Bioavailability: ~50%
Half-life elimination: ~9 days
Time to peak, plasma: ~1 day
Excretion: aqueous humor

**Drug-drug interaction**
verteporfin photodynamic therapy
pegloticase

**Common Side effects**
Conjunctival hemorrhage, eye pain, vitreous floaters, increased intraocular pressure
Anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, corneal edema, eye discharge, eye irritation, eye pain, hypertension, increased intraocular pressure (IOP), ocular discomfort, punctate keratitis, reduced visual acuity, visual disturbance, vitreous floaters, vitreous opacities

**Serious allergic and hypersensitivity**
No
No

**Pregnancy**
Use only if clearly needed
Category B; use only if clearly needed

**Lactation**
Use with caution
Use with caution

**Storage and stability**
Store at 2–8°C (36–46°F)

**How supplied**
1 single-use container with 0.05 mL of 10 mg/mL ranibizumab (0.5 mg dose prefilled syringe or vial) or 6 mg/mL ranibizumab (0.3 mg dose vial)
Sterile foil pouch with a single-use glass syringe pre-filled with 0.3 mg of drug in a 90 µL volume pack.

**References:**

19. Medical Review Criteria Guideline for Managing Care (Apollo) 2013. Age-Related Macular Degeneration (AMD/ARMD) Therapy
20. Medical Review Criteria Guideline for Managing Care (Apollo) 2013. AMD Intraocular Injection Treatments (Macugen, Lucentis)

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<tr>
<td>05/17/2017</td>
<td>• Revised criteria for Lucentis to include FDA approved indications of:</td>
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