Medication Policy Manual

Policy No: dru267

Topic: Eylea®, aflibercept

Date of Origin: January 13, 2012

Committee Approval Date: May 12, 2017

Next Review Date: May 2018

Effective Date: June 1, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Aflibercept (Eylea) is an inhibitor of vascular endothelial growth factor (VEGF) that is injected directly into the eye to prevent the formation of new blood vessels and reduce blood vessel leakage and inflammation.
Policy/Criteria

I. Most contracts require prior authorization approval of aflibercept (Eylea) prior to coverage. Aflibercept (Eylea) may be considered medically necessary when criteria A and B below are met:

A. At least one of the following diagnostic criteria 1, 2, or 3 below are met (See Appendix 1). Must have a diagnosis of:
   1. Neovascular (wet) age-related macular degeneration (wAMD).
      OR
   2. Macular edema associated with retinal vein occlusion (RVO).
      OR
   3. Diabetic retinopathy with macular edema (DME).

AND

B. Treatment with intravitreal bevacizumab (Avastin®) has been ineffective, not tolerated, or is contraindicated.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx does not consider aflibercept (Eylea) to be a self-administered medication.

B. Authorization may be reviewed annually to confirm that current medical necessity criteria are met and that the medication is effective as supported by clinical documentation indicating stabilization or improvement in vision.

III. Aflibercept (Eylea) is considered investigational when used for all other conditions, including but not limited to:

- Central serous retinopathy
- Cystoid macular degeneration
- Diabetic retinopathy not associated with diabetic macular edema
- Glaucoma associated vascular disorders
- Macular edema not associated with retinal vein occlusion
- Pathologic myopia
- Radiation maculopathy
- Retinal neovascularization
- In combination with other VEGF inhibitors, including but not limited to bevacizumab (Avastin), pegaptanib (Macugen), and ranibizumab (Lucentis)
Position Statement
- Bevacizumab (Avastin) is the best value VEGF inhibitor for the treatment of ocular conditions. Bevacizumab (Avastin) does not require prior authorization for ocular conditions.

- Although aflibercept (Eylea), bevacizumab (Avastin), and ranibizumab (Lucentis) have different indications, in clinical trials they have demonstrated evidence of efficacy for maintaining or improving visual acuity across various retinal disorders.

- Aflibercept (Eylea), bevacizumab (Avastin), and ranibizumab (Lucentis) all work using the same mechanism of action by binding to the receptor binding site of active forms of VEGF-A. Likely because of similarities in mechanism of action, studies have not been able to demonstrate that one product is superior to another in efficacy or safety.

- Evidence-based recommendations and clinical guidelines do not differentiate the VEGF inhibitors in clinical practice recommendations. Evidence-based recommendations and clinical guidelines equally recommend the use of VEGF inhibitors, including bevacizumab (Avastin), for the treatment of wAMD, macular edema secondary to RVO, and DME (including diabetic retinopathy associated with DME).

- Aflibercept (Eylea) is currently being studied in other vascular related ocular conditions. The clinical benefit of aflibercept (Eylea) in these indications is uncertain to date.

- Ziv-aflibercept (Zaltrap) is approved for use in cancer indications and is not equivalent to, or interchangeable with aflibercept (Eylea).

- Previous concerns over the use of compounded or repackaged products such as bevacizumab (Avastin) have been alleviated by the FDA’s 2013 Drug Quality and Security Act, which provides better oversight of compounding pharmacies. In addition, the American Society of Retina Specialists has published online safety information about compounding pharmacies to help retina specialists choose high-quality providers of bevacizumab (Avastin). Furthermore, in February 2015 the FDA issued Draft Guidance regarding drug compounding and repackaging of biologics to further standardize quality of bevacizumab (Avastin). [1-3]

Clinical Efficacy

Neovascular (wet) Age-related Macular Degeneration (wAMD)
- The efficacy and safety of aflibercept (Eylea) in the treatment of wAMD was evaluated in two randomized, non-inferiority studies versus ranibizumab (Lucentis). At week 52 aflibercept (Eylea) showed similar efficacy to ranibizumab (Lucentis) in maintaining visual acuity. [4]

- There is moderate certainty that aflibercept (Eylea), bevacizumab (Avastin), and ranibizumab (Lucentis) are similarly effective for maintaining or improving vision when used in the treatment of wAMD. There are high quality systematic reviews that do not conclude one treatment is superior to another. There are individual trials of fair confidence that the comparators have similar efficacy.

  * One high quality systematic review of bevacizumab (Avastin) in the treatment of wAMD concluded that it improves visual acuity and central retinal thickness (moderate correlate to visual acuity) and is more effective than photodynamic therapy (without verteporfin). [5]
One high quality systematic review of VEGF inhibitors concluded that pegaptanib (Macugen) and ranibizumab (Lucentis) reduce the risk of visual acuity loss in patients with wAMD. It also concluded that ranibizumab (Lucentis) may improve visual acuity; however, the review did not include trials which evaluated bevacizumab (Avastin) or aflibercept (Eylea). [6]

The American Academy of Ophthalmology (AAO) guidelines recommend aflibercept (Eylea), bevacizumab (Avastin) or ranibizumab (Lucentis) for the treatment of wAMD. The AAO does not recommend the use of pegaptanib (Macugen) in this condition due to evidence demonstrating that it does not improve visual acuity on average in patients with new onset wAMD unlike other currently available VEGF inhibitors. [7]

**Diabetic Macular Edema (DME)**

Aflibercept (Eylea) has demonstrated improvements in visual acuity when used for the treatment of DME and diabetic retinopathy associated with DME.

Aflibercept (Eylea) was compared to focal/grid photocoagulation in a phase II trial for 24 weeks in the treatment of DME and was shown to produce a clinically relevant improvement in visual acuity. This effect was sustained at 52 weeks. [8,9]

Based on a follow-up analysis of two phase III clinical trials, aflibercept (Eylea) was also shown to be more effective in reducing the severity of diabetic retinopathy in patients with DME after 100 weeks of treatment relative to laser therapy. [10]

There is moderate certainty that VEGF inhibitors improve visual acuity in patients with DME; however, there is insufficient evidence to demonstrate that one VEGF inhibitor is clinically superior to another based on one systematic review and one government-sponsored comparative study.

A Cochrane systematic review concluded that aflibercept (Eylea), bevacizumab (Avastin), and ranibizumab (Lucentis) are more effective than laser photocoagulation in improving visual acuity. There was insufficient power to detect a difference between each of the VEGF inhibitors included in the review. [11]

A government-sponsored trial evaluated mean improvement in visual acuity in patients with DME treated with aflibercept (Eylea), bevacizumab (Avastin) or ranibizumab (Lucentis) when administered on an as needed basis. [12]

- The trial concluded that there was no clinically meaningful difference in improvement in visual acuity in the overall DME population.
- It was noted that aflibercept (Eylea) was modestly more effective (approximate mean improvement of 6 letters) at improving visual acuity relative to the other VEGF inhibitors in a subset of patients with lower baseline visual acuity at the 1- and 2-year follow-up.
- However, there was low confidence in the trial results due to an imbalance in concomitant treatment between study arms, potential for bias as investigators were not blinded to treatment, and the reduced number of doses given to patients in the bevacizumab (Avastin) and ranibizumab (Lucentis) arms than would otherwise have been given if a fixed dose regimen was used.

The AAO support the use of VEGF inhibitors, including aflibercept (Eylea), bevacizumab (Avastin), and ranibizumab (Lucentis) for the treatment of DME (including diabetic retinopathy associated with DME). [13]
* AAO recommendations were based on trials comparing aflibercept (Eylea), bevacizumab (Avastin), and ranibizumab (Lucentis) to focal laser treatment (READ-2, BOLT, AND DA VINICI studies, respectively). All trials showed that treatment with VEGF inhibitors resulted in statistically and clinically significant improvements in visual acuity in patients with DME after one to two years of treatment compared to laser treatment.

* In the BOLT study, bevacizumab (Avastin) was also shown to reduce the level of severity of diabetic retinopathy in patients with DME over the 12-month treatment period whereas the severity remained relatively stable in patients who received laser therapy. [14]

**Retinal Vein Occlusion**

* Aflibercept (Eylea) has been shown to improve visual acuity compared to sham injections in clinical trials of patients with macular edema following RVO.

* In patients with macular edema due to central retinal vein occlusion (CRVO), eyes treated with aflibercept (Eylea) gained a mean of 17.3 letters in best-corrected visual acuity vs. sham-treated eyes which lost 4.0 letters (P < 0.001) after 24 weeks of treatment. This gain was maintained through week 52. [15,16]

* A similar magnitude of benefit was reported in a second study in patients also with macular edema due to CRVO. [17]

* In patients with macular edema secondary to branch retinal vein occlusion (BRVO), a greater proportion of subjects (26%) who received aflibercept (Eylea) for 24 weeks achieved ≥ 15 letters of improvement versus those who received laser photocoagulation. [18]

* There is moderate certainty that VEGF inhibitors [aflibercept (Eylea), bevacizumab (Avastin), pegaptanib (Macugen), and ranibizumab (Lucentis)] are more effective than sham injection or laser therapy in maintaining or improving visual acuity in patients with macular edema secondary to RVO based on two Cochrane systematic reviews; however, there is insufficient evidence to demonstrate that one VEGF inhibitor is clinically superior to another due to the lack of direct comparative evidence.

* Evidence-based recommendations from UptoDate and the Centers for Medicare and Medicaid Services support the use of anti-VEGFs [aflibercept (Eylea), bevacizumab (Avastin), and ranibizumab (Lucentis)] for the treatment of macular edema secondary to RVO. [19,20]

**Other Uses**

* Trials of aflibercept (Eylea) in a variety of other conditions such as radiation retinopathy, central serous chorioretinopathy, and pathologic myopia are ongoing and are considered investigational due to lack of published, high quality data. The efficacy and safety of aflibercept (Eylea) has not been evaluated in patients with diabetic retinopathy not associated with DME and macular edema not associated with RVO.

* The use of aflibercept (Eylea) in conjunction with other VEGF inhibitors, including bevacizumab (Avastin), pegaptanib (Macugen) or ranibizumab (Lucentis) is considered investigational as there is no evidence evaluating the efficacy or safety of aflibercept (Eylea) when used in this manner.
Safety

- There is low certainty in the evidence demonstrating differences in adverse events between intravitreous VEGF inhibitors.
  
  * A meta-analysis evaluating the cardiovascular (CV) safety of intravitreal VEGF inhibitors in patients with wAMD, DME, or RVO concluded that VEGF inhibitors, specifically bevacizumab (Avastin) and ranibizumab (Lucentis), are not associated with a significant increase in risk of systemic CV and bleeding events or in overall mortality, stroke, or CV mortality in elderly patients. However, the studies and meta-analysis were not sufficiently powered to correctly assess these risks. [21]

  * The trial conducted by the CATT research group comparing ranibizumab (Lucentis) to bevacizumab (Avastin) for the treatment of wet AMD found the following regarding safety: [22,23]
    - A statistically significant difference was seen at 52 weeks in the rates of serious systemic adverse events between the ranibizumab (Lucentis) and bevacizumab (Avastin) groups (19.0% vs 24.1%, P = 0.04).
    - A significant difference was also seen at 2 years [39.9% bevacizumab (Avastin) vs 31.7% ranibizumab (Lucentis); adjusted risk ratio 1.30; 95% CI: 1.07, 1.57; P = 0.009].
    - This difference was largely due to hospitalizations for infections such as pneumonia and urinary tract infections. It is uncertain if these events were related to either medication.

- Intravitreal VEGF inhibitors have also been associated with inflammation, blurred vision, corneal edema, eye discharge and irritation, and hypertension. [24]

- Additional serious adverse effects reported with intravitreous VEGF inhibitors include endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. After injection, patients should be advised to seek immediate care if the treated eye becomes red, painful, sensitive to light, or they notice a change in vision. [24]

- Bevacizumab (Avastin) is listed in national treatment guidelines and is recognized by the Centers for Medicare and Medicaid Services as a safe and effective treatment option for wet AMD, DME and RVO. [25]

  * Bevacizumab (Avastin), when used in the eye, must be extemporaneously compounded to achieve the appropriate dose. In 2011, a group of cases of endophthalmitis were reported with the use of bevacizumab (Avastin) which was determined to be the result of unsafe practices by one compounding pharmacy. [2,26,27]

  * All intravitreal injections, including aflibercept (Eylea), pegaptanib (Macugen), ranibizumab (Lucentis), and bevacizumab (Avastin), are associated with the risk of endophthalmitis. [24,28,29]

Dosing [24]

- Aflibercept (Eylea) 2 mg is injected intravitreously (into the eye) every 4 weeks for 12 weeks, then every 8 weeks.

- Bevacizumab (Avastin) 1.25 mg is injected intravitreously (into the eye) monthly or as needed.
- Pegaptanib (Macugen) 0.3 mg is injected intravitreously (into the eye) every 6 weeks.
- Ranibizumab (Lucentis) 0.5 mg is injected intravitreously (into the eye) every 1 to 3 months.

Appendix 1: List of covered diagnoses [20,30,31]

<table>
<thead>
<tr>
<th>Covered Diagnosis</th>
<th>Synonyms</th>
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<tbody>
<tr>
<td>Neovascular (wet) age-related macular degeneration</td>
<td>Exudative senile macular degeneration</td>
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<td></td>
<td>Age-related macular degeneration (ARMD)</td>
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<tr>
<td></td>
<td>Choroidal neovascularization (CNV)</td>
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<tr>
<td>Diabetic Macul Edema and Diabetic Retinopathy</td>
<td>Diabetic macular edema (DME) associated with diabetic retinopathy</td>
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<td></td>
<td>DME due to Type 1 or Type 2 diabetic retinopathy</td>
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<tr>
<td></td>
<td>DME due to nonproliferative or proliferative diabetic retinopathy (mild, moderate, or severe)</td>
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<tr>
<td></td>
<td>Center involving diabetic macular edema</td>
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<td></td>
<td>Diabetic retinal edema</td>
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<td>Clinically significant diabetic macular edema (CSME)</td>
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<td>Myopic choroidal neovascularization</td>
<td>Choroidal neovascularization secondary to pathologic myopia (mCNV)</td>
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<tr>
<td>Macular edema associated with Retinal Vein Occlusion</td>
<td>Macular edema associated with central retinal vein occlusion (CRVO)</td>
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<tr>
<td></td>
<td>Macular edema associated with branch retinal vein occlusion (BRVO)</td>
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<tr>
<td></td>
<td>Macular edema associated with tributary (branch) retinal vein occlusion</td>
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Cross References

Avastin®, bevacizumab, OmedaRx Medication Policy Manual, Policy No. 215

Lucentis®, ranibizumab, OmedaRx Medication Policy Manual, Policy No. 242

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
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<td>E11.329</td>
<td>Diabetic retinopathy</td>
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<td>ICD-10</td>
<td>E11.311</td>
<td>Diabetic macular edema</td>
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<td>ICD-10</td>
<td>H35.053</td>
<td>Retinal neovascularization not otherwise specified</td>
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<td>ICD-10</td>
<td>H34.9</td>
<td>Retinal vascular occlusion</td>
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<td>ICD-10</td>
<td>H35.32</td>
<td>Exudative senile macular degeneration of retina</td>
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<td>H40.89</td>
<td>Glaucoma associated vascular disorders</td>
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<td>ICD-10</td>
<td>H35.8</td>
<td>Macular edema</td>
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References

   http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm


**Revision History**

<table>
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<th>Revision Date</th>
<th>Revision Summary</th>
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<tr>
<td>05/12/2017</td>
<td>No change to intent of coverage criteria. Annual reauthorization changed to “may.”</td>
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<tr>
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