VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS FOR OPHTHALMIC USE

Policy Number: 2012D0001A
Effective Date: January 1, 2014

Table of Contents:

<table>
<thead>
<tr>
<th>Category</th>
<th>Page</th>
<th>Cross Reference Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLICY DESCRIPTION</td>
<td>2</td>
<td>ZALTRAP® (Ziv-aflibercept), 2013M0034A</td>
</tr>
<tr>
<td>COVERAGE RATIONALE/CLINICAL CONSIDERATIONS</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>REGULATORY STATUS</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>CLINICAL EVIDENCE</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>APPLICABLE CODES</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>REFERENCES</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>POLICY HISTORY/REVISION INFORMATION</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

INSTRUCTIONS:

“Medical Policy assists in administering UCare benefits when making coverage determinations for members under our health benefit plans. When deciding coverage, all reviewers must first identify enrollee eligibility, federal and state legislation or regulatory guidance regarding benefit mandates, and the member specific Evidence of Coverage (EOC) document must be referenced prior to using the medical policies. In the event of a conflict, the enrollee's specific benefit document and federal and state legislation and regulatory guidance supersede this Medical Policy. In the absence of benefit mandates or regulatory guidance that govern the service, procedure or treatment, or when the member's EOC document is silent or not specific, medical policies help to clarify which healthcare services may or may not be covered. This Medical Policy is provided for informational purposes and does not constitute medical advice. In addition to medical policies, UCare also uses tools developed by third parties, such as the InterQual Guidelines®, to assist us in administering health benefits. The InterQual Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. Other Policies and Coverage Determination Guidelines may also apply. UCare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary and to provide benefits otherwise excluded by medical policies when necessitated by operational considerations.”
POLICY DESCRIPTION:

This policy provides information on a specialty medication known as VEGF (Vascular Endothelial Growth Factor) Inhibitors. Intravitreal administration (injection into the eye) of VEGF inhibitors are used to treat people with age related macular degeneration (AMD). AMD is characterized by the abnormal formation of new blood vessels (neovascularization) and swelling in the retina and iris. Macular degeneration is a disease commonly associated with aging, diabetes, and glaucoma, that gradually destroys sharp, central vision. Central vision is needed for seeing objects clearly and for common daily tasks such as reading and driving. This policy addresses the following medications: Bevacizumab (Avastin®), Pegatanib (Macugen®), Ranibizumab (Lucentis®), and Aflibercept (Eylea®).

COVERAGE RATIONALE / CLINICAL CONSIDERATIONS:

• Bevacizumab (Avastin®) intravitreal injections are considered REASONABLE AND MEDICALLY NECESSARY for the treatment of patients with a diagnosis of:
  1. Neovascular (wet) age-related macular degeneration (AMD).
  2. Background/proliferative diabetic retinopathy.
  3. Diabetic macular edema.
  4. Macular edema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).
  5. Retinal neovascularization.
  7. Choroidal neovascularization secondary to pathologic myopia, angiodysplasia/pseudoxanthoma elasticum, or ocular histoplasmosis syndrome (OHS).

• Pegatanib (Macugen®) intravitreal injections are considered REASONABLE AND MEDICALLY NECESSARY in patients with a diagnosis of neovascular (wet) age-related macular degeneration (AMD) and diabetic retinopathy with macular edema.

• Ranibizumab (Lucentis®) intravitreal injections are considered REASONABLE AND MEDICALLY NECESSARY for the treatment of patients with a diagnosis of:
  1. Neovascular (wet or exudative) age-related macular degeneration (AMD).
  2. Diabetic retinopathy with macular edema.
  3. Diagnosis of macular edema following retinal vein occlusion.

• Aflibercept (Eylea®) intravitreal injections are considered REASONABLE AND MEDICALLY NECESSARY for the treatment of patients with a diagnosis of:
  1. Neovascular (wet or exudative) age-related macular degeneration (AMD).
  2. Diagnosis of macular edema following retinal vein occlusion.

• Concurrent therapy of VEGF inhibitors or combination with photodynamic therapy (PDT) with verteporfin (Visudyne®) is considered NOT MEDICALLY NECESSARY for intraocular use, due to inadequate clinical evidence of safety and/or efficacy in published, peer-reviewed medical literature.

• All other ophthalmic uses of ranibizumab (Lucentis®), pegaptanib sodium (Macugen®), bevacizumab (Avastin®), and aflibercept (Eylea®) are considered EXPERIMENTAL/INVESTIGATIONAL.

Clinical trials of the VEGF inhibitors for the treatment of wet age-related macular degeneration, diabetic
Clinical Considerations:

- Intravitreal VEGF injections are an office administered injection. This is not considered a self-administered medication.
- There are neither adequate nor well-controlled studies in pregnant women. VEGF should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. VEGF has not been studied in pediatric populations.
- VEGF injections are contraindicated in patients with ocular or periocular infections, active intraocular inflammation, and a known hypersensitivity to aflibercept or any of the excipients in Eylea®.

Recommended Dosing:

- **Aflibercept (Eylea®)**: 2 mg is injected intravitreously every 4 weeks for 12 weeks, then every 8 weeks (additional efficacy was not demonstrated when Eylea® was dosed every 4 weeks compared to every 8 weeks). Aflibercept is available as Eylea® in a 2mg/0.05mL solution for injection.

- **Ranibizumab (Lucentis®)**: 0.5 mg is injected intravitreously (into the eye) monthly. It is supplied in a single-dose vial.

- **Pegaptanib sodium (Macugen®)**: 0.3 mg is injected intravitreously (into the eye) every 6 weeks. The safety and efficacy of pegaptanib sodium (Macugen®) administered to both eyes concurrently have not been studied. It is supplied in a single-dose vial.

- **Bevacizumab (Avastin®)**: Is not FDA-approved for use in ophthalmic indications; however, a large body of medical literature supports its off-label use for wet-AMD at a much lower cost. It is injected every 4-6 weeks. When used for these indications, bevacizumab must be compounded. Compounding pharmacies must comply with United States Pharmacopeia (USP) Chapter 797, which sets standards for the compounding, transportation, and storage of compounded sterile products (CSP). The Pharmacy Compounding Accreditation Board can verify that the pharmacy is adhering to these standards.

- **Side effects**: Intravitreous VEGF inhibitors include eye pain, injection-site bleeding, vitreous floaters, cataracts, and an increase in eye pressure. Serious adverse effects reported include endophthalmitis, retinal detachment, and iatrogenic traumatic cataract.

BACKGROUND:

Age-related macular degeneration (AMD) is a leading cause of blindness in the United States, a progressive degenerative disease of the eyes that causes the deterioration of photoreceptors in the central portion of the retina, afflicting with blindness approximately 15 million people in the United States.

As AMD progresses, it develops into a "dry" form (non-neovascular) or a "wet" form (neovascular). The dry form of AMD is more common and leads to a slow deterioration of the macula with a gradual loss of vision.
over a period of years. The wet form of the disease is responsible for the majority of cases with severe vision loss and is characterized by abnormal growth of new blood vessels across the posterior of the eye (behind the retina), a process known as choroidal neovascularization (CNV). These blood vessels are fragile and often leak blood and serum, damaging the macular area of the retina and interfering with central vision.

The development of these abnormal blood vessels is due in part to the activity of vascular endothelial growth factor (VEGF), a naturally occurring protein in the body that stimulates and/or increases the growth, proliferation, permeability, and inflammation of blood vessels, with progression of the neovascular (wet) form of AMD. Wet AMD is also referred to as vascular, neovascular, and exudative.

The family of VEGF consists of multiple members; however, VEGF-A and placental growth factor (PGF) are predominately linked with the pathology and development of age-related macular degeneration. The activity of VEGF-A is primarily mediated by 2 receptor tyrosine kinases, VEGF receptor-1 and VEGF receptor-2. The angiogenetic factor, PGF, has the ability to bind to VEGF receptor 1 to effectively stimulate angiogenesis and increase vascular permeability in leukocytes. In addition, the up-regulation of PGF correlates with the promotion of leukocyte chemotaxis and increased recruitment of inflammatory cells into the retina, thus increasing promotion of inflammatory factors.

**Pegaptanib sodium (Macugen®):** The first intra-vitreal VEGF agent approved by the United States Food and Drug Administration (FDA) for wet AMD was pegaptanib (Macugen®), a messenger RNA aptamer and VEGF antagonist. Pegaptanib binds to VEGF and inhibits its binding to cellular receptors; its anti-VEGF activity is expected to inhibit abnormal blood vessel proliferation and thus decrease the vision loss associated with the proliferation of abnormal blood vessels. However, the number of patients whose visual acuity improved with pegaptanib was limited, so the agent is no longer widely used.\(^{28}\)

Currently, the most common treatments for wet AMD are intra-vitreal bevacizumab (Avastin®) and ranibizumab (Lucentis®).

**Bevacizumab (Avastin®):** Is a recombinant humanized monoclonal IgG1 antibody. Bevacizumab binds to vascular endothelial growth factor (VEGF) and inhibits its interaction to receptors on the surface of endothelial cells. In the process, it prevents the proliferation of endothelial cells and formation of new blood vessels. Several studies of intra-vitreal bevacizumab have shown improvement in visual acuity that is similar to the improvement with ranibizumab. Intra-vitreal bevacizumab, when given monthly, can maintain the vision of more than 90% of patients with wet AMD.

**Ranibizumab (Lucentis®):** Is a recombinant humanized monoclonal antibody fragment with specificity for all isoforms of human VEGF. It is used for the treatment of patients with neovascular (wet) AMD and macular edema following retinal vein occlusion. Ranibizumab binds to and inhibits vascular endothelial growth factor (VEGF-A) from promoting growth of new blood vessels beneath the retina. It is injected directly into the vitreous portion of the eye once monthly. 34-40% of Lucentis®-treated members experienced a clinically significant improvement in vision, defined as gaining 15 or more letters after one year.

**Afiblercept (Eylea®):** Is a recombinant humanized monoclonal IgG1 antibody fragment also known as VEGF Trap-Eye. It is engineered to bind all isoforms of VEGF-A, VEGF-B, PGF, and prevent their binding to VEGFR-1 and/or VEGFR-2. Inhibiting the binding to these receptors decreases inflammation, vascular permeability, mitogenic activity, leukocyte chemotaxis, and further progression of neovascular AMD with loss of vision. Afiblercept appears to have a greater binding affinity to VEGF-A isoforms compared with other native receptors, thus inhibiting the activation of the receptors and effectively suppressing the VEGF-regulated
disruption of the blood-retinal barrier and stimulation of blood vessel formation and growth. Although all VEGF inhibitors (aflibercept, bevacizumab, pegaptanib, and ranibizumab) target VEGF, the mechanism of action through which the functional pathway is inhibited varies. Aflibercept functions as a VEGF and PGF decoy, pegaptanib is a short RNA oligonucleotide that assumes a specific 3D structure and binds to target molecules with high affinity (also known as aptamer therapy), and ranibizumab and bevacizumab are antibodies directed at VEGF. The net result of all these drugs is decreased VEGF activity, which then results in decreased vision loss. Ranibizumab, pegaptanib, and aflibercept are currently FDA approved for treatment of neovascular AMD, but bevacizumab is used off-label because of its lower cost.

REGULATORY STATUS:

1. **U.S. FOOD AND DRUG ADMINISTRATION (FDA):**
   - **Aflibercept (Eylea®):** On November 18, 2011, the FDA approved aflibercept ophthalmic solution (Eylea®, Regeneron Pharmaceuticals Inc.) for the treatment of neovascular (wet) AMD. The FDA’s approval of Eylea® was based on positive results from the 2 phase III VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) trials.
   - **Pegaptanib sodium (Macugen®):** Approved by the FDA on December 17, 2004, as a selective VEGF antagonist for the treatment of neovascular (wet) AMD. Supplemental approvals for pegaptanib have since been issued by the FDA.
   - **Ranibizumab (Lucentis®):** Was initially approved by the FDA on June 30, 2006, as a vascular endothelial growth factor A (VEGF-A) antagonist, for the treatment of neovascular (wet) AMD. It received a supplemental approval from the FDA in June 2010 for use in the treatment of macular edema following retinal vein occlusion.
   - **Bevacizumab (Avastin®):** Is FDA approved as first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum, metastatic HER2/neu negative breast cancer, glioblastoma, non-squamous non-small cell lung cancer, recurrent ovarian cancer, and metastatic renal cell carcinoma. The oncology indications for bevacizumab listed here for information only. Administration of bevacizumab infusions or intravitreal injections for the treatment of neovascular age-related macular degeneration and macular edema is considered off-label.

2. **CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS):**
   Medicare does not have a National Coverage Determination (NCD) for aflibercept (Eylea®), ranibizumab (Lucentis®), or pegaptanib sodium (Macugen®).
   Medicare does not have Local Coverage Determinations (LCD) for aflibercept (Eylea®), ranibizumab (Lucentis®), or pegaptanib sodium (Macugen®).
   There are Local Coverage Determinations and local Articles for intravitreal use of BEVACIZUMAB (Avastin®). When used for ophthalmological purposes, documentation must demonstrate the medical necessity for use, clearly indicating the rationale for treatment. CMS currently allows payment for BEVACIZUMAB (Avastin®). 32

3. **MINNESOTA DEPARTMENT OF HUMAN SERVICES (DHS):**
   Minnesota DHS does not have a policy statement regarding aflibercept (Eylea®), ranibizumab
(Lucentis®), or pegaptanib sodium (Macugen®) in its Provider Manual or other specific provider references.

**CLINICAL EVIDENCE:**

1. **EVIDENCE FROM AVAILABLE PUBLISHED STUDIES:**

   **Pegaptanib sodium (Macugen®):**
   
   Gragoudas et al (2004) reported the results of 2 concurrent, prospective, randomized, double-blind, multi-center, dose-ranging, controlled clinical trials (n = 1,186) on the use of pegaptanib in the treatment of neovascular AMD. Intravitreous injection into 1 eye per patient of pegaptanib (at a dose of 0.3 mg, 1.0 mg, or 3.0 mg) or sham injections were administered every 6 weeks over a period of 48 weeks, for a total of 9 treatments. The primary end point was the proportion of patients who had lost fewer than 15 letters of visual acuity at 54 weeks. In the group given pegaptanib at 0.3 mg, 70 % of patients lost fewer than 15 letters of visual acuity, as compared with 55 % among the controls (p < 0.001). The risk of severe loss of visual acuity (loss of 30 letters or more) was reduced from 22 % in the sham-injection group to 10 % in the group receiving 0.3 mg of pegaptanib (p < 0.001). More patients receiving pegaptanib (0.3 mg), as compared with sham injection, maintained their visual acuity or gained acuity (33 % versus 23 %; p = 0.003). As early as 6 weeks after beginning therapy with the study drug, and at all subsequent points, the mean visual acuity among patients receiving 0.3 mg of pegaptanib was better than in those receiving sham injections (p < 0.002). Dose levels above 0.3 mg did not demonstrate any additional benefit. On average, Macugen (0.3) mg treated patients and sham treated patients continued to experience vision loss. However, the rate of vision decline in the Macugen treated group was slower than the rate in the patients who received sham treatment. Among the adverse events that occurred, endophthalmitis (1.3 % of patients), traumatic

   A 2-year phase III study demonstrated that pegaptanib sodium improved vision in persons with diabetic macular edema (Pfizer, 2010). The study included 260 subjects who received 0.3 mg pegaptanib sodium or a sham procedure consisting of anesthesia and a simulated injection in the eye every 6 weeks for a total of 9 injections in year 1. In year 2, subjects received injections as often as every 6 weeks based on pre-specified criteria. Up to 3 focal or grid laser treatments per year were permitted beginning at week 18, at the investigator’s discretion. The primary outcome measure of the study was the proportion of subjects who, after 1 year, experienced an improvement in vision from baseline of 2 lines, or 10 letters, on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart. The investigators reported that 37 % of subjects treated with pegaptanib sodium gained 2 lines, or 10 letters, of vision on the ETDRS eye chart at 54 weeks, versus 20 % of subjects who received the sham procedure (p = 0.0047). On average, subjects treated with pegaptanib sodium gained 5.2 letters of vision at year 1 compared to 1.2 letters for subjects receiving sham (p < 0.05). At the end of year 2, subjects receiving pegaptanib sodium had gained on average 6.1 letters of vision compared to 1.3 letters for subjects in the sham arm of the study (p < 0.01). The investigators reported that adverse events were consistent with those observed in clinical trials of pegaptanib sodium in persons with neovascular age-related macular degeneration and similar to clinical experience with pegaptanib sodium.

   **Ranibizumab (Lucentis®):**
   
   The FDA approval of Lucentis is based on data from 2 phase III clinical studies (MARINA and ANCHOR). In these studies, nearly all patients (about 95 %) treated with Lucentis (0.5 mg) maintained (defined as
the loss of less than 15 letters in VA) and up to 40 % improved (defined as the gain of 15 letters or more in VA) vision at 1-year, as measured on the Early Treatment of Diabetic Retinopathy eye chart. On average, patients treated with Lucentis in the MARINA study experienced an improvement from baseline of 6.6 letters at 2-year compared to a loss of 14.9 letters in the sham group. In the ANCHOR study, patients treated with Lucentis, on average, experienced an 11.3 letter gain from baseline at 1-year compared to a loss of 9.5 letters in the Visudyne photodynamic therapy control group. Up to 40 % of patients treated with Lucentis achieved vision of 20/40 or better.

In June 2010, the FDA approved Lucentis (ranibizumab injection) for the treatment of macular edema following retinal vein occlusion (RVO). The FDA approval was based upon 2 randomized controlled clinical studies -- the BRAVO study, which assessed the safety and efficacy profile of ranibizumab in a total of 397 patients with macular edema following branch-RVO, and the CRUISE study, which assessed the safety and efficacy profile of ranibizumab in a total of 392 patients with macular edema following central- RVO. During the first 6-month period, participants in both trials received monthly injections of either 0.3 mg or 0.5 mg of ranibizumab (n = 527) or monthly sham injections (n = 262). The primary endpoint of both studies was mean change from baseline in best corrected visual acuity (BCVA) at 6 months compared with patients receiving sham injections. In the BRAVO study, the percentage of patients in the ranibizumab 0.5 mg study arm who gained 15 or more letters in BCVA from baseline at month 6 was 61 % (compared with 29 % in the sham injection arm). In the CRUISE study, the percentage of patients in the ranibizumab 0.5 mg study arm who gained 15 or more letters in BCVA from baseline at month 6 was 48 % (compared with 17 % in the sham injection arm). At month 6, patients in BRAVO who received 0.5 mg of ranibizumab had a mean gain of 18.3 letters (compared to 7.3 letters in patients receiving sham injections). In the CRUISE study, at month 6, patients who received 0.5 mg of ranibizumab had a mean gain of 14.9 letters (compared to 0.8 letters for patients receiving sham injections).

An NIH-sponsored, multi-center, randomized clinical trial demonstrated that ranibizumab in combination with macular laser photocoagulation is superior to macular laser photocoagulation alone at 12 months of follow-up (Diabetic Retinopathy Clinical Research Network, 2010). The need for re-treatment was determined by retinal thickness as measured by optical coherence tomography (OCT) and visual acuity. The 1-year mean change in the visual acuity letter score from baseline was significantly greater in the ranibizumab + prompt laser group (+9, p < 0.001) and ranibizumab + deferred laser group (+9, p < 0.001) but not in the triamcinolone + prompt laser group (+4, p = 0.31) compared with the sham + prompt laser group (+3). Intravitreal ranibizumab with prompt or deferred laser is more effective through at least 1 year compared with prompt laser alone for the treatment of DME involving the central macula.

A second single-center, randomized clinical trial also demonstrated that intravitreal injection of bevacizumab every 6 weeks based on clinical response determined by OCT and visual acuity is superior to macular photocoagulation every 4 months (Michaelides et al, 2010). The authors reported the odds of gaining greater than or equal to 10 ETDRS letters over 12 months were 5.1 times greater in the bevacizumab group than in the laser group (adjusted odds ratio, 5.1; 95 % confidence interval [CI]: 1.3 to 19.7; p = 0.019).

In a comparative, retrospective case series, Fong et al (2010) compared VA outcomes after bevacizumab or ranibizumab treatment for AMD. These researchers followed 452 patients in a retrospective study of exudative AMD treated with anti-VEGF drugs; 324 patients were treated with bevacizumab and 128 patients with ranibizumab. All treatment naive patients who received either
bevacizumab or ranibizumab were followed for 1 year. Baseline characteristics and VA were recorded using standard descriptive statistics. Main outcome measure was VA. At 12 months, the distribution of VA improved in both groups with 22.9 % of bevacizumab and 25.0 % of ranibizumab attaining greater than or equal to 20/40. Improvement in vision was observed in 27.3 % of the bevacizumab group and 20.2 % of the ranibizumab group. The mean number of injections at 12 months was 4.4 for bevacizumab and 6.2 for ranibizumab. There were 8 (2 %) deaths in the bevacizumab group and 4 (3 %) in the ranibizumab group. Two patients developed endophthalmitis in the bevacizumab group and the ranibizumab group. The bevacizumab group had slightly worse acuity at baseline, but both groups showed improvement and stability of vision over time. The authors concluded that both treatments seem to be effective in stabilizing VA loss. There was no difference in VA outcome between the 2 treatment groups. Because the study is a non-randomized comparison, selection bias could mask a true treatment difference. Results from the Comparison of the Age-related Macular Degeneration Treatment Trials (CATT) will provide more definitive information about the comparative effectiveness of these drugs.

In a multi-center, single-blind, non-inferiority trial, Martin and colleagues/the CATT Research Group (2011) randomly assigned 1,208 patients with neovascular AMD to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in VA at 1 year, with a non-inferiority limit of 5 letters on the eye chart. Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm, p = 0.03 by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab (p > 0.20). The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1 % versus 19.0 %; risk ratio, 1.29; 95 % confidence interval [CI]: 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern. The authors concluded that at 1 year, bevacizumab and ranibizumab had equivalent effects on VA when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events require further study.

Aflibercept (Eylea®):

Eylea® was found to be as effective as the VEGF inhibitor ranibizumab (Lucentis®, Genentech/Roche) in two clinical trials involving 2,457 adults. FDA’s approval of Eylea® was based on positive results from the 2 phase III VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) trials. Both found the drug non-inferior to ranibizumab, which is currently the most potent FDA-approved treatment option for wet AMD.

In VIEW 1 (n = 1,217), conducted in the United States, and VIEW 2 (n = 1,240), conducted in Europe, all regimens of the drug, including 2 mg dosed every 2 months (after 3 loading doses), successfully met the primary endpoint of statistical non-inferiority compared with ranibizumab. The proportions of patients who maintained or improved vision over the course of 52 weeks in VIEW 1 were 96 %, 95 %, and 95 %
of patients receiving aflibercept 0.5 mg monthly, 2.0 mg monthly, and 2.0 mg every 2 months, respectively. This compared with 94% of patients receiving the standard 0.5-mg monthly dose of ranibizumab. For the secondary endpoint, visual acuity, the new drug was better. Patients receiving 2 mg monthly had a greater mean improvement in visual acuity at week 52, with a gain of 10.9 letters compared with 8.1 letters with ranibizumab (p < 0.01). All other dose groups were not significantly different from ranibizumab with respect to this secondary endpoint.

In VIEW 2, vision was maintained in 96% of all aflibercept dose groups and in 94% of the ranibizumab group. All doses were statistically non-inferior to ranibizumab, and no differences were noted between the drugs in visual acuity gain. The most commonly reported AEs in patients receiving aflibercept included eye pain, conjunctival hemorrhage, vitreous floaters, cataract, and an increase in eye pressure. Aflibercept should not be used in those who have an active eye infection or active ocular inflammation. It has not been studied in pregnant women, so the treatment should be used only in pregnant women if the potential benefits of the treatment outweigh any potential risks. Age-related macular degeneration does not occur in children and aflibercept has not been studied in children. The recommended dose is 2 mg every 4 weeks (monthly) for the first 12 weeks, followed by 2 mg every 8 weeks (2 months).

In a multi-center, randomized, double-blinded study, Heier et al (2011) evaluated vision outcomes, injection frequency, and safety during the as-needed (PRN) treatment phase of a study evaluating a 12-week fixed dosing period followed by PRN dosing to week 52 with VEGF Trap-Eye for neovascular (wet) AMD. A total of 159 patients with subfoveal choroidal neovascularization (CNV) secondary to wet AMD were included in this study. Patients were randomly assigned to 1 of 5 intra-vitreal VEGF Trap-Eye treatment groups: 0.5 mg or 2 mg every 4 weeks or 0.5, 2, or 4 mg every 12 weeks during the fixed-dosing period (weeks 1 to 12). From weeks 16 to 52, patients were evaluated monthly and were retreated PRN with their assigned dose (0.5, 2, or 4 mg). Main outcome measures included change in central retinal/lesion thickness (CR/LT), change in total lesion and CNV size, mean change in BCVA, proportion of patients with 15-letter loss or gain, time to first PRN injection, re-injection frequency, and safety at week 52. The decrease in CR/LT at week 12 versus baseline remained significant at weeks 12 to 52 (-130 μm from baseline at week 52) and CNV size regressed from baseline by 2.21 mm at 48 weeks². After achieving a significant improvement in BCVA during the 12-week, fixed-dosing phase for all groups combined, PRN dosing for 40 weeks maintained improvements in BCVA to 52 weeks (5.3-letter gain; p < 0.0001). The most robust improvements and consistent maintenance of VA generally occurred in patients initially dosed with 2 mg every 4 weeks for 12 weeks, demonstrating a gain of 9 letters at 52 weeks. Overall, a mean of 2 injections was administered after the 12-week fixed-dosing phase, and the mean time to first re-injection was 129 days; 19% of patients received no injections and 45% received 1 or 2 injections. Treatment with VEGF Trap-Eye was generally safe and well-tolerated, with few ocular or systemic adverse effects (AEs). The authors concluded that PRN dosing with VEGF Trap-Eye at weeks 16 to 52 maintained the significant anatomic and vision improvements established during the 12-week fixed-dosing phase with a low frequency of re-injections. Repeated dosing with VEGF Trap-Eye was well-tolerated over 52 weeks of treatment.
### APPLICABLE CODES:

The Current Procedural Terminology (CPT®) codes and HCPCS codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other medical policies and coverage determination guidelines may apply.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9257</td>
<td>Injection, Bevacizumab, 0.25 mg</td>
</tr>
<tr>
<td>C9291</td>
<td>Injection, Aflibercept, 2 mg vial</td>
</tr>
<tr>
<td>J2503</td>
<td>Injection, Pegaptanib sodium, 0.3 mg</td>
</tr>
<tr>
<td>J2778</td>
<td>Injection, Ranibizumab, 0.1 mg (new 1-1-2008)</td>
</tr>
<tr>
<td>J9035</td>
<td>Injection, Bevacizumab, 10 mg</td>
</tr>
<tr>
<td>Q2046</td>
<td>Injection, aflibercept, 1 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPT® Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>67028</td>
<td>Intravitreal injection of a pharmacologic agent (separate procedure)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>362.52</td>
<td>Exudative senile macular degeneration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-9 Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>362.01</td>
<td>Background diabetic retinopathy</td>
</tr>
<tr>
<td>362.02</td>
<td>Proliferative diabetic retinopathy</td>
</tr>
<tr>
<td>362.03</td>
<td>Nonproliferative diabetic retinopathy NOS</td>
</tr>
<tr>
<td>362.04</td>
<td>Mild nonproliferative diabetic retinopathy</td>
</tr>
<tr>
<td>362.05</td>
<td>Moderate nonproliferative diabetic retinopathy</td>
</tr>
<tr>
<td>362.06</td>
<td>Severe nonproliferative diabetic retinopathy</td>
</tr>
<tr>
<td>362.07</td>
<td>Diabetic macular edema</td>
</tr>
<tr>
<td>362.15</td>
<td>Retinal telangiectasia</td>
</tr>
<tr>
<td>362.29</td>
<td>Other nonidiabetic proliferative retinopathy</td>
</tr>
<tr>
<td>362.30</td>
<td>Retinal vascular occlusion unspecified</td>
</tr>
<tr>
<td>362.35</td>
<td>Central vein occlusion of retina</td>
</tr>
<tr>
<td>362.36</td>
<td>Venous tributary (branch) occlusion of retina</td>
</tr>
<tr>
<td>362.52</td>
<td>Exudative senile macular degeneration of retina</td>
</tr>
<tr>
<td>362.53</td>
<td>Cystoid macular degeneration of retina</td>
</tr>
<tr>
<td>362.83</td>
<td>Retinal edema</td>
</tr>
<tr>
<td>362.84</td>
<td>Retinal ischemia</td>
</tr>
<tr>
<td>364.42</td>
<td>Rubeosis iridis</td>
</tr>
<tr>
<td>365.63</td>
<td>Glaucoma associated with vascular disorders of eye</td>
</tr>
<tr>
<td>365.89</td>
<td>Other specified glaucoma</td>
</tr>
</tbody>
</table>

**ICD-9-CM 362.16 requires a secondary code describing its cause:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>115.02</td>
<td>Histoplasma Capsulatum retinitis</td>
</tr>
<tr>
<td>115.12</td>
<td>Histoplasma Duboisii retinitis</td>
</tr>
<tr>
<td>115.92</td>
<td>Histoplasmosis retinitis unspecified</td>
</tr>
<tr>
<td>360.21</td>
<td>Progressive high (degenerative) myopia</td>
</tr>
<tr>
<td>362.16</td>
<td>Retinal neovascularization NOS</td>
</tr>
</tbody>
</table>

CPT® is a registered trademark of the American Medical Association.
REFERENCES:


**POLICY HISTORY:**

<table>
<thead>
<tr>
<th>DATE</th>
<th>ACTION/DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/24/2013</td>
<td>New policy 2012D0001A. Approved by the Interim Medical Policy Committee.</td>
</tr>
<tr>
<td>05/13/2013</td>
<td>Reviewed and approved by the Pharmacy and Therapeutic Committee (P&amp;T).</td>
</tr>
<tr>
<td>11/15/2013</td>
<td>Published to UCare.org</td>
</tr>
</tbody>
</table>