**OPHTHALMOLOGIC POLICY**

Vascular Endothelial Growth Factor (VEGF) Inhibitors

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**INSTRUCTIONS FOR USE**

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care 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.

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**COVERAGE RATIONALE**

This policy provides information about the use of certain specialty pharmacy medications administered by the intravitreal route for ophthalmologic conditions.

This policy refers to the following drug products, all of which are vascular endothelial growth factor (VEGF) inhibitors:

- aflibercept (Eylea™)
- bevacizumab (Avastin®)
- pegaptanib (Macugen®)
- ranibizumab (Lucentis®)

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Ophthalmologic Policy (VEGF Inhibitors): Drug Policy (Effective 02/01/2014)

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Proven Uses:

- Aflibercept is **proven** for the treatment of
  1. neovascular age-related macular degeneration (AMD)
  2. macular edema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)
- Bevacizumab is **proven** for the treatment of
  1. neovascular age-related macular degeneration (AMD)
  2. diabetic macular edema
  3. macular edema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)
  4. proliferative diabetic retinopathy
  5. neovascular glaucoma
  6. choroidal neovascularization secondary to pathologic myopia, angioid streaks/pseudoxanthoma elasticum, or ocular histoplasmosis syndrome (OHS)
- Pegaptanib is **proven** for the treatment of
  1. neovascular age-related macular degeneration (AMD)
  2. diabetic macular edema
- Ranibizumab is **proven** for the treatment of
  1. neovascular age-related macular degeneration (AMD)
  2. diabetic macular edema
  3. macular edema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)
  4. choroidal neovascularization secondary to pathologic myopia, angioid streaks/pseudoxanthoma elasticum, or ocular histoplasmosis syndrome (OHS)

Unproven Use:

Aflibercept, bevacizumab, pegaptanib, and ranibizumab are **unproven** for the treatment of retinopathy of prematurity.

Because VEGF is involved in a wide variety of physiologic processes, the ocular and systemic safety of anti-VEGF agents is of prime concern in neonates.

Additional Information:

Bevacizumab is supplied in sterile vials containing a solution of 25 mg/mL. Doses utilized in ophthalmic conditions generally range from 6.2 mcg to 2.5 mg. Therefore, bevacizumab in vials is often divided into single-dose, prefilled syringes for intravitreal use by compounding pharmacies. 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.

Please refer to the US Food and Drug Administration (FDA) Section of this policy for information related to contamination of compounded bevacizumab. In an effort to guard against contamination during the compounding process, the United States Veterans Health Administration (USVHA) requires that only USVHA pharmacies may dispense bevacizumab for intravitreal administration to Veterans Administration beneficiaries. The medication must be dispensed directly to the VA ophthalmologist, who will then be responsible for preparing and administering the bevacizumab dose for each patient. In addition to strict labeling and storage requirements, the ophthalmologists is required to prepare only one dose of medication from each vial; if both eyes are to be treated, a separate vial and syringe must be utilized.

Centers for Medicare and Medicaid Services (CMS):

Medicare does not have a National Coverage Determination (NCD) for bevacizumab (Avastin).
In general, Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf

Local Coverage Determinations (LCDs) for bevacizumab (Avastin) do exist. Refer to the LCDs for Drugs and Biologicals Bevacizumab (Avastin) and Intravitreal Bevacizumab (Avastin). (Accessed September 11, 2013)

Medicare does not have a National Coverage Determination (NCD) for Eylea. In general, Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf

Local Coverage Determinations (LCDs) for Eylea do not exist at this time. (Accessed September 11, 2013)

Medicare does not have a National Coverage Determination (NCD) for Lucentis. In general, Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf

Local Coverage Determinations (LCDs) for ranibizumab (Lucentis) do exist. Refer to the LCDs for Ranibizumab (Lucentis). (Accessed September 11, 2013)

Medicare does not have a National Coverage Determination (NCD) for Macugen. In general, Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf

Local Coverage Determinations (LCDs) for Macugen do exist. Refer to the LCDs for Macugen (Pegaptanib Sodium injection). (Accessed September 11, 2013)

**BENEFIT CONSIDERATIONS**

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

**BACKGROUND**

Vascular endothelial growth factor (VEGF) is a protein that stimulates the growth, proliferation and survival of vascular endothelial cells. VEGF plays a critical role in the development of new blood vessels (angiogenesis), increases vascular permeability in small blood vessels and prevents apoptosis of vascular endothelial cells in immature blood vessels. VEGF has been implicated in blood retinal barrier breakdown and pathological ocular neovascularization.⁴
CLINICAL EVIDENCE

Proven Uses:
Neovascular age-related macular degeneration
Aflibercept, pegaptanib, and ranibizumab are indicated for the treatment of neovascular age-related macular degeneration.\(^5\)\(^-\)\(^7\)

The safety and efficacy of aflibercept were evaluated in two randomized, multi-center, double-masked active-controlled studies (VIEW-1 and VIEW-2) in patients with neovascular AMD (n=2,412). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (A2Q8); 2) aflibercept administered 2 mg every 4 weeks (A2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (A0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (R0.5Q4). The primary endpoint in each study was visual acuity after 1 year of treatment. Both A2Q8 and A2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group.\(^5\)

The safety and efficacy of pegaptanib were evaluated in two controlled, double-masked, and identically designed randomized studies (EOP1003 and EOP1004) in patients with neovascular AMD (n=1,190).\(^6\) Patients were randomized to receive intravitreous injections of placebo, 0.3 mg pegaptanib, 1 mg pegaptanib, or 3 mg pegaptanib administered every 6 weeks for the first year. The patients were then re-randomized between treatment and no treatment during the second year. The primary endpoint in each study was the proportion of patients losing less than 15 letters of visual acuity after 1 year of treatment. Results showed that treatment with pegaptanib demonstrated statistically significant less vision loss compared to placebo [Study EOP1003, pegaptanib 73% vs. placebo 60%; Study EOP1004, pegaptanib 67% vs. placebo 53% (P<.0001)]. On average, continued vision loss was observed in the groups receiving pegaptanib 0.3 mg and placebo. However, the rate of vision decline in the pegaptanib treated group was slower than the rate in the patients who received placebo. Pegaptanib was less effective during the second year than during the first year. The percentage of patients losing less than 15 letters from baseline to week 102 was: Study EOP1003, pegaptanib 38/67 (57%); placebo 30/54 (56%); Study EOP1004, pegaptanib 40/66 (61%); placebo 18/53 (34%).

The safety and efficacy of ranibizumab were assessed in three randomized, double-masked, placebo- or active-controlled studies (AMD-1, AMD-2, and AMD-3) in patients with neovascular AMD (n=1,323).\(^7\) AMD-1 enrolled patients with minimally classic or occult choroidal neovascularization (CNV), while AMD-2 enrolled those with predominantly classic CNV. In AMD-1, subjects received monthly injections of ranibizumab 0.3 mg (n=238), ranibizumab 0.5 mg (n=240), or placebo (n=238) for 24 months. In AMD-2, patients received monthly ranibizumab 0.3 mg plus placebo photodynamic therapy (PDT) (n=140), monthly ranibizumab 0.5 mg plus placebo PDT (n=140), or monthly placebo injections plus active verteporfin PDT (n=143) for 12 months. Placebo or active PDT regimens were administered with the first injection, then every three months if fluorescein angiography revealed persistent or recurrent leakage. The primary efficacy endpoint for both studies was maintained visual acuity (loss of <15 letters) at 12 months. Data met this endpoint for the 0.5 mg dose in both AMD-1 (95%, vs. 62% for placebo; p<0.01) and AMD-2 (96% vs. 64% for verteporfin PDT; p<0.01). Both trials also demonstrated significant efficacy in a pair of secondary endpoints: the portion of subjects gaining at least 15 letters of acuity (AMD-1: 34% vs. 5%, p<0.01; AMD-2: 40% vs. 6%, p<0.01); and mean change in visual acuity (AMD-1: +7.2 letters, vs. -10.5 letters, p<0.01; AMD-2: +11.3 letters, vs. -9.5 letters, p<0.01). AMD-1 showed maintained efficacy through 24 months in the primary (90% vs. 53%, p<0.01) and both secondary endpoints (33% vs. 4%, p<0.01; +6.6 letters vs. -14.9 letters, p<0.01). AMD-3 enrolled 184 patients with neovascular AMD with or without classic CNV. Study subjects received ranibizumab 0.3 mg (n=60), ranibizumab 0.5 mg (n=61), or placebo (n=63) monthly for 3 months, followed by injections every 3 months through 12 months. Primary efficacy, measured by mean change in visual acuity, indicated that the 3 monthly doses of ranibizumab produced improvements in visual acuity; once dosing was transferred to once-every-three-month dosing, visual acuity returned to baseline values, but were maintained without significant worsening,
compared to a loss of acuity for placebo at 12 months (-0.2 letters vs. -16.3 letters). Almost 90% of ranibizumab-treated subjects maintained their visual acuity at the completion of the study period.

In a multicenter, prospective, noninferiority, double-masked, randomized clinical trial, the relative efficacy and safety profile of bevacizumab versus ranibizumab intravitreal injections for the treatment of neovascular age-related macular degeneration (AMD) was evaluated.6,7 Patients (n=501) aged ≥50 years were eligible if they presented with subfoveal neovascular AMD, with best-corrected visual acuity (BVCA) in the study eye of between 20/32 and 20/320 measured on the Early Treatment of Diabetic Retinopathy Study chart, and a lesion area of less than 12 optic disc areas (DA). Subjects were randomly assigned to intravitreal administration of bevacizumab (1.25 mg) or ranibizumab (0.50 mg), then followed for one year. A loading dose of three monthly intravitreal injections was administered to all subjects, followed by an as-needed regimen (one injection in case of active disease) for the remaining 9 months with monthly follow-up. The main outcome measure was the mean change in visual acuity at one year, with a noninferiority limit of five letters. In the per protocol analysis, bevacizumab was noninferior to ranibizumab (bevacizumab minus ranibizumab +1.89 letters; 95% confidence interval [CI], -1.16 to +4.93, p<0.0001). The intention-to-treat analysis was concordant. The mean number of injections was 6.8 in the bevacizumab group and 6.5 in the ranibizumab group (p=0.39). Both drugs reduced the central subfield macular thickness, with a mean decrease of 95 μm for bevacizumab and 107 μm for ranibizumab (p=0.27). There were no significant differences in the presence of subretinal or intraretinal fluid at final evaluation, dye leakage on angiogram, or change in choroidal neovascular area. The proportion of patients with serious adverse events was 12.6% in the bevacizumab group and 12.1% in the ranibizumab group (p=0.88). The proportion of patients with serious systemic or ocular adverse events was similar in both groups. Based on these results, bevacizumab was determined to be noninferior to ranibizumab for visual acuity at one year with similar safety profiles. Ranibizumab tended to have a better anatomic outcome.

A multi-center, single-blind, non-inferiority study was conducted by the CATT Research Group in 1,208 patients with neovascular age-related macular degeneration (AMD).8 Participants were randomly assigned to receive intravitreal injections of either ranibizumab or bevacizumab on a monthly schedule or as needed with monthly evaluations. The primary outcome of the study was the mean change in visual acuity at one year, with a non-inferiority limit of 5 letters on the eye chart. The investigators reported that monthly administration of bevacizumab was equivalent to monthly administration of ranibizumab, with 8.0 and 8.5 letters gained, respectively. Results of as needed administration of the agents were determined to be equivalent, with bevacizumab recipients gaining 5.9 letters and ranibizumab recipients gaining 6.8 letters. Ranibizumab as needed was equivalent to monthly ranibizumab, while 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 treatment (p>0.20). However, the proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern. Therefore, the investigators recommended that differences in rates of serious adverse events should be further studied. At one year, bevacizumab and ranibizumab had equivalent effects on visual acuity 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.

Tufail et al. evaluated the efficacy and safety of intravitreal bevacizumab injections for the treatment of neovascular age related macular degeneration in a prospective, double-blind, multicenter, randomized controlled trial of 131 patients.9 Participants were randomized to receive either three 1.25 mg bevacizumab loading injections at six week intervals followed by further treatment if required at six week intervals or the standard treatment available at the start of the trial (photodynamic treatment with verteporfin for predominantly classic type neovascular age...
related macular degeneration, or intravitreal pegaptanib or placebo treatment for occult or minimally classic type neovascular age related macular degeneration. The primary outcome was the proportion of patients achieving at least 15 letters of visual acuity at one year (54 weeks). The secondary outcome measure was the proportion of patients with stable vision and the mean change in visual acuity. In the bevacizumab group, 21 (32%) patients gained 15 or more letters from baseline visual acuity compared with two (3%) in the standard care group (p<0.001). In addition, the proportion of patients who lost fewer than 15 letters of visual acuity from baseline was significantly greater among those receiving bevacizumab treatment (91% (59) vs. 67% (44) in standard care group; p<0.001). Mean visual acuity increased by 7.0 letters in the bevacizumab group (median of seven injections) compared with a decrease of 9.4 letters in the standard care group (p<0.001). The initial improvement at week 18 (plus 6.6 letters) was sustained to week 54. There were no reported cases of endophthalmitis or serious uveitis related to the intervention in the bevacizumab group (n=65). The investigators concluded that bevacizumab 1.25 mg intravitreous injections given as part of a weekly variable retreatment regimen is superior to standard care, with low rates of serious ocular adverse events.

An interventional, consecutive, prospective case series of 102 eyes in 102 patients was conducted to evaluate the short-term efficacy of bevacizumab in patients with neovascular age-related macular degeneration.10 Patients received monthly intravitreal bevacizumab (IVB) until resolution of macular edema, subretinal fluid, and/or pigment epithelial detachment. The primary outcome measures included visual acuity (VA) and CRT (central retinal thickness) as measured by OCT (optical coherence tomography). Baseline Mean VA was 20/80 and CRT was 251.0 ± 74.6 μm. Patients were evaluated at 6, 10, and 14 weeks. Results: Mean VA=20/63 (p<0.001), 20/50 (p<0.001), and 20/50 (p<0.001); mean CRT=214.9 ± 41.7 μm, 204.8 ± 33.6 μm, and 210 μm (p<0.05) at 6, 10, and 14 weeks respectively. IVB appears to be beneficial and well tolerated in the short term for AMD. Although these results are promising larger, randomized, placebo-controlled studies are needed to confirm these results.

A prospective, open-label, nonrandomized clinical study was conducted on 60 patients with neovascular age-related macular degeneration.11 The primary outcome measure was proportion of eyes losing <15 letters of vision after 12 months. Fifty one patients completed the 12 month study. Mean visual acuity improved from 45.7 letters at baseline to 53.1 letters at 12 months (p=0.004) and 47 eyes (92.2%) lost <15 letters. Although the study concluded that patients treated with bevacizumab had significant anatomical and functional improvement, further long-term, larger, randomized studies are needed to confirm efficacy.

**Diabetic Macular Edema**

Ranibizumab is indicated for the treatment of diabetic macular edema.7 The safety and efficacy of ranibizumab in diabetic macular edema (DME) were assessed in two randomized, double-masked, 3-year studies. Patient age ranged from 21 to 91 years, with a mean age of 62 years. A total of 759 patients (ranibizumab 0.3 mg, n=250; ranibizumab 0.5 mg, n=252; placebo, n=257) were enrolled, with 582 (77%) completing through Month 36. In Studies DME-1 and DME-2, patients received monthly ranibizumab 0.3 mg or 0.5 mg intravitreal injections or monthly placebo injections during the 24-month controlled treatment period. From Months 25 through 36, patients who previously received placebo were eligible to receive monthly ranibizumab 0.5 mg, and patients originally randomized to monthly ranibizumab 0.3 mg or 0.5 mg continued to receive their assigned dose. All patients were eligible for macular focal/grid laser treatment beginning at Month 3 of the 24-month treatment period or panretinal photocoagulation (PRP) as needed. Through Month 24, macular focal/grid laser treatment was administered in 94 of 250 (38%) patients treated with ranibizumab 0.3 mg and 185 of 257 (72%) patients treated with placebo; PRP was administered in 2 of 250 (1%) patients treated with ranibizumab 0.3 mg and 30 of 257 (12%) patients treated with placebo. Compared to monthly ranibizumab 0.3 mg, no additional benefit was observed with monthly treatment with ranibizumab 0.5 mg. VA outcomes observed at Month 24 in patients treated with ranibizumab 0.3 mg were maintained with continued treatment through Month 36 in both DME studies. Patients in the placebo arms who received ranibizumab 0.5 mg
beginning at Month 25 achieved lesser VA gains compared to patients who began treatment with ranibizumab at the beginning of the studies.

Michaelides et al. conducted a prospective, randomized, masked, single-center, 2-year, 2-arm clinical trial in 80 eyes of 80 patients to compare repeated intravitreal bevacizumab (IVB) and modified Early Treatment of Diabetic Retinopathy Study (ETDRS) macular laser therapy (MLT) in patients with persistent clinically significant diabetic macular edema. Participants were randomized to receive either IVB (6 weekly; minimum of 3 injections and maximum of 9 injections in the first 12 months) or MLT (4 monthly; minimum of 1 treatment and maximum of 4 treatments in the first 12 months). The primary end point was the difference in ETDRS best-corrected visual acuity (BCVA) at 12 months between the bevacizumab and laser groups. The baseline mean ETDRS BCVA was 55.7 ± 9.7 (range 34–69) in the bevacizumab group and 54.6 ± 8.6 (range 36–68) in the laser group. The mean ETDRS BCVA at 12 months was 61.3 ± 10.4 (range 34–79) in the bevacizumab group and 50.0 ± 16.6 (range 8–76) in the laser group (p=0.0006). Furthermore, the bevacizumab group lost a median of 0.5 ETDRS letters (p=0.0002). The odds of gaining ≥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, 1.3–19.7; p=0.019). At 12 months, central macular thickness decreased from 507 ± 145 μm (range 281–900 μm) at baseline to 378 ± 134 μm (range 167–699 μm) (p<0.001) in the IVB group, whereas it decreased to a lesser extent in the laser group, from 481 ± 121 μm (range 279–844 μm) to 413 ± 135 μm (range 170–708 μm) (p=0.02). The median number of injections was 9 in the IVB group, and the median number of laser treatments was 3 in the MLT group. The study provides evidence to support the use of bevacizumab in patients with center-involving CSME without advanced macular ischemia.

In a randomized, three-arm clinical trial, Soheilian et al. studied 103 eyes with a history of DME without previous treatment. Eyes were randomized to receive either intravitreal bevacizumab (IVB) (n=37), bevacizumab plus triamcinolone (IVB/IVT) (n=33), and macular laser photocoagulation (n=33). Visual acuity changes (primary outcome measure) in the groups were statistically significant in the groups at both 6 weeks (p<0.0001) and 12 weeks (p<0.024). The significant treatment effect was only demonstrated in the IVB only at both 6 and 12 weeks and in the IVB/IVT group at just 6 weeks. Central macular thickness was not statistically significantly reduced in the groups. Conclusion is that IVB for patients with DME obtained better visual acuity results at 12 weeks than photocoagulation did. No further beneficial effect of intravitreal triamcinolone was demonstrated.

Sultan et al. conducted a randomized, multicenter, parallel-group trial to confirm safety and compare efficacy of intravitreal pegaptanib sodium versus placebo in subjects with diabetic macular edema (DME) involving the center of the macula associated with vision loss not due to ischemia. During year one of the study, subjects received pegaptanib 0.3 mg or placebo every 6 weeks (total = 9 injections) and were eligible to receive focal/grid photocoagulation beginning at week 18. Subjects received injections as often as every 6 weeks per pre-specified criteria in the second year of the study. The primary efficacy endpoint was the proportion of subjects gaining ≥10 letters of visual acuity (VA) from baseline to year one. In total, 260 (pegaptanib, n=133; placebo, n=127) and 207 (pegaptanib, n=107; placebo, n=100) subjects were included in years 1 and 2 intent-to-treat analyses, respectively. A total of 49 of the 133 (36.8%) subjects from the pegaptanib group and 25 of the 127 (19.7%) from the placebo group experienced a VA improvement of ≥10 letters at week 54 compared with baseline (odds ratio [OR], 2.38; 95% confidence interval, 1.32–4.30; p=0.0047). In the pegaptanib-treated subjects, change in mean VA from baseline by visit was superior (p<0.05) to sham at weeks 6, 24, 30, 36, 42, 54, 78, 84, 90, 96, and 102. At week 102, pegaptanib-treated subjects gained, on average, 6.1 letters versus 1.3 letters for placebo (p<0.01). Fewer pegaptanib- than placebo-treated subjects received focal/grid laser treatment (week 54, 31/133 [23.3%] vs 53/127 [41.7%], respectively, p=0.002; week 102, 27/107 [25.2%] vs 45/100 [45.0%], respectively, p=0.003). The pegaptanib treatment group showed significantly better results on the National Eye Institute-Visual Functioning Questionnaire than sham for subscales important in this population. Pegaptanib was well tolerated; the
frequencies of discontinuations, adverse events, treatment-related adverse events, and serious adverse events were comparable in the pegaptanib and placebo groups.

In a randomized, double-masked, multicenter, dose-ranging, controlled trial, Cunningham et al. evaluated the safety and efficacy of pegaptanib sodium injection in the treatment of diabetic macular edema (DME).15 Study subjects (n=172) included those with a best-corrected visual acuity (VA) between 20/50 and 20/320 in the study eye, DME involving the center of the macula, and for whom the investigator judged photocoagulation could be safely withheld for 16 weeks. The primary outcome measures were best-corrected VA, central retinal thickness at the center point of the central subfield as assessed by optical coherence tomography measurement, and the need for additional therapy with photocoagulation between weeks 12 and 36. Intravitreous pegaptanib 0.3 mg (n=44), pegaptanib 1 mg (n=44), pegaptanib 3 mg (n=42), or placebo (n=42) injections were administered upon study entry, at week 6, and at week 12 with additional injections and/or focal photocoagulation as needed for another 18 weeks. Final assessments were conducted at week 36. Median VA was better at week 36 with 0.3 mg (20/50), as compared with placebo (20/63) (p=0.04). A larger proportion of those receiving 0.3 mg gained VAs of ≥10 letters (approximately 2 lines) (34% vs. 10%, p=0.003) and ≥15 letters (18% vs. 7%, p=0.12). Mean central retinal thickness decreased by 68 microm with 0.3 mg, versus an increase of 4 microm with placebo (p=0.02). Larger proportions of those receiving 0.3 mg had an absolute decrease of both ≥100 microm (42% vs. 16%, p=0.02) and ≥75 microm (49% vs. 19%, p=0.008). Photocoagulation was deemed necessary in fewer subjects in each pegaptanib arm (0.3 mg vs. placebo, 25% vs. 48%; p=0.04). All pegaptanib doses were well tolerated. Endophthalmitis occurred in 1 of 652 injections (0.15% per injection; i.e., 1/130 [0.8%] pegaptanib subjects) and was not associated with severe visual loss. Overall, subjects assigned to pegaptanib had better VA outcomes, were more likely to show reduction in central retinal thickness, and were deemed less likely to need additional therapy with photocoagulation at follow-up.

Mitchell et al. conducted a 12-month, randomized, double-masked, multicenter, laser-controlled phase III study that included 345 patients aged ≥18 years, with type 1 or 2 diabetes mellitus and visual impairment due to DME.16 Patients were randomized to ranibizumab + placebo laser (n=116), ranibizumab + laser (n=118), or placebo injections + laser (n=111). Ranibizumab/placebo was given for 3 months then as needed; laser/sham laser was given at baseline then as needed (patients had scheduled monthly visits). The main outcome measures were mean average change in BCVA from baseline to month 1 through 12 and safety of ranibizumab. Ranibizumab alone and combined with laser were superior to laser monotherapy in improving mean average change in BCVA letter score from baseline to month 1 through 12 (+6.1 and +5.9 vs +0.8; both p<0.0001). At month 12, a significantly greater proportion of patients had a BCVA letter score ≥15 and BCVA letter score level >73 (20/40 Snellen equivalent) with ranibizumab (22.6% and 53%, respectively) and ranibizumab + laser (22.9% and 44.9%) versus laser alone (8.2% and 23.6%). The mean central retinal thickness was significantly reduced from baseline with ranibizumab (-118.7 μm) and ranibizumab + laser (-128.3 μm) versus laser alone (-61.3 μm; both p<0.001). Patients received ~7 (mean) ranibizumab/sham injections over 12 months. No endophthalmitis cases occurred. Increased intraocular pressure was reported for 1 patient each in the ranibizumab arms. Ranibizumab monotherapy or combined with laser was not associated with an increased risk of cardiovascular or cerebrovascular events in this study. Ranibizumab monotherapy and combined with laser provided superior visual acuity gain over standard laser in patients with visual impairment due to DME. Visual acuity gains were associated with significant gains in VFQ-25 scores. At 1 year, no differences were detected between the ranibizumab and ranibizumab + laser arms. Ranibizumab monotherapy and combined with laser had a safety profile in DME similar to that in age-related macular degeneration.

In a 12-month, multicenter, placebo-controlled, double-masked study, Massin et al. investigated the safety and efficacy of ranibizumab in DME involving the foveal center.17 Subjects were randomly assigned to intravitreal ranibizumab (0.3 or 0.5 mg; n=51 each) or placebo (n=49). The treatment schedule comprised three monthly injections, after which treatment could be
stopped/reinitiated with an opportunity for rescue laser photocoagulation (protocol-defined criteria). After month one, dose-doubling was permitted according to protocol-defined criteria. Efficacy (BCVA and CRT) and safety were compared between pooled ranibizumab and placebo arms using the full analysis set (n=151, patients receiving≥1 injection). At month 12, BCVA improved from baseline by 10.3 ± 9.1 letters with ranibizumab and declined by 1.4 ± 14.2 letters with placebo (p<0.0001). Mean CRT reduction was 194.2 ± 135.1 μm with ranibizumab and 48.4 ± 153.4 μm with placebo (p<0.0001). Gain of ≥10 letters BCVA from baseline occurred in 60.8% of ranibizumab and 18.4% of placebo eyes (p<0.0001). Safety data were consistent with previous studies of intravitreal ranibizumab. The investigators concluded that ranibizumab is effective in improving BCVA and is well tolerated in DME. Future clinical trials are required to confirm its long-term efficacy and safety.

The Diabetic Retinopathy Clinical Research Network evaluated intravitreal 0.5 mg ranibizumab or 4 mg triamcinolone combined with focal/grid laser versus focal/grid laser alone for treatment of diabetic macular edema (DME) in a multicenter, randomized clinical trial. A total of 854 study eyes of 691 participants with visual acuity of 20/32 to 20/320 and DME involving the fovea were randomized to placebo injection + prompt laser (n=293), 0.5 mg ranibizumab + prompt laser (n=187), 0.5 mg ranibizumab + deferred (≥24 weeks) laser (n=188), or 4 mg triamcinolone + prompt laser (n=186). The main outcome measures were best-corrected visual acuity and safety after one year of treatment. The 1-year mean change in the visual acuity letter score from baseline was significantly greater in the ranibizumab + prompt laser group (+9+/−11, p<0.001) and ranibizumab + deferred laser group (+9+/−12, p<0.001) but not in the triamcinolone + prompt laser group (+4+/−13, p=0.31) compared with the placebo + prompt laser group (+3+/−13). Reduction in mean central subfield thickness in the triamcinolone + prompt laser group was similar to both ranibizumab groups and greater than in the placebo + prompt laser group. In the subset of pseudophakic eyes at baseline (n=273), visual acuity improvement in the triamcinolone + prompt laser group appeared comparable to that in the ranibizumab groups. No systemic events attributable to study treatment were apparent. Three eyes (0.8%) had injection-related endophthalmitis in the ranibizumab groups, whereas elevated intraocular pressure and cataract surgery were more frequent in the triamcinolone + prompt laser group. Two-year visual acuity outcomes were similar to 1-year outcomes. The researchers concluded that 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.

Nguyen et al. compared ranibizumab with focal/grid laser or a combination of both in diabetic macular edema (DME) in a prospective, randomized, interventional, multicenter clinical trial of 126 patients. Subjects were randomized 1:1:1 to receive 0.5 mg of ranibizumab at baseline and months 1, 3, and 5 (group 1, n=42), focal/grid laser photocoagulation at baseline and month 3 if needed (group 2, n=42), or a combination of 0.5 mg of ranibizumab and focal/grid laser at baseline and month 3 (group 3, n=42). The primary end point was the change from baseline in best-corrected visual acuity (BCVA) at month 6. At month 6, the mean gain in BCVA was significantly greater in group 1 (+7.24 letters, p=0.01, analysis of variance) compared with group 2 (-0.43 letters), and group 3 (+3.80 letters) was not statistically different from groups 1 or 2. For patients with data available at 6 months, improvement of 3 lines or more occurred in 8 of 37 (22%) in group 1 compared with 0 of 38 (0%) in group 2 (p=0.002) and 3 of 40 (8%) in group 3. Excess foveal thickness was reduced by 50%, 33%, and 45% in groups 1, 2, and 3, respectively. During a span of 6 months, ranibizumab injections by the current protocol had a significantly better visual outcome than focal/grid laser treatment in patients with DME.

**Macular Edema Secondary to BRVO/CRVO**

Aflibercept is indicated for the treatment of macular edema following central retinal vein occlusion (CRVO). The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, placebo-controlled studies (COPERNICUS and GALILEO) in patients with macular edema following CRVO (n=358). The primary endpoint of both studies was the proportion of patients who gained at least 15 letters in BCVA compared to baseline.
In the COPERNICUS study, 189 eyes with macular edema secondary to CRVO were randomized 3:2 to receive aflibercept or placebo monthly for 6 months. At week 24, 56.1% of eyes treated with aflibercept gained 15 letters or more from baseline versus 12.3% of placebo-treated eyes (p<0.001). The aflibercept-treated eyes gained a mean of 17.3 letters versus placebo-treated eyes, which lost 4.0 letters (p<0.001). Central retinal thickness decreased by 457.2 µm in eyes treated with aflibercept versus 144.8 µm in placebo-treated eyes (p<0.001). Progression to any neovascularization occurred in 0 and 5 (6.8%) of eyes treated with aflibercept and placebo, respectively (p=0.006). Conjunctival hemorrhage, reduced visual acuity, and eye pain were the most common adverse events (AEs). Serious ocular AEs were reported by 3.5% of aflibercept patients and 13.5% of placebo patients.

In the GALILEO study, 177 patients were randomized to 2 mg aflibercept or placebo injections every 4 weeks for a total of 52 weeks. Beginning at Week 24 and continuing through week 52, patients in the aflibercept group were treated on an as-needed basis with placebo injections on non-treatment visits. Patients in the placebo group continued to receive placebo injections every 4 weeks. At Week 52, 60.2% of patients in the aflibercept group gained at least 15 ETDRS letters from baseline, compared with 32.4% of patients in the placebo group (p=0.0004). Patients receiving aflibercept gained a mean of 16.9 letters compared with a gain of 3.8 letters for patients receiving placebo (p<0.0001). Patients receiving aflibercept experienced a significantly larger mean decrease in CRT compared with patients receiving placebo (-423.5 µm vs -219.3 µm; p<0.0001). Aflibercept was generally well tolerated; the most common ocular adverse events were macular edema, increased intraocular pressure and eye pain.

Ranibizumab is indicated for the treatment of macular edema following retinal vein occlusion (RVO). The safety and efficacy of ranibizumab were assessed in two randomized, double-masked, one-year studies (RVO-1 and RVO-2) in patients with macular edema following RVO (n=789). The primary endpoint of both studies was best-corrected visual acuity (BCVA), as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

In Study RVO-1, patients with macular edema following branch or hemi-RVO, received monthly ranibizumab 0.3 mg (n=134), ranibizumab 0.5 mg (n=131), or placebo (n=132) injections for 6 months. All patients were eligible for rescue laser treatment beginning at Month 3 of the 6 month treatment period. Rescue laser treatment was given to 26 (20%) patients treated with 0.5 mg ranibizumab and 72 (55%) patients who received placebo. Monthly injections could be continued during the observation period (6 to 12 months) if pre-specified criteria were met. At baseline, mean BCVA was 54.6 letters (range, 16 to 79). After 6 months, BCVA significantly improved in both the ranibizumab 0.3 mg group by 16.6 ±11 letters (95% confidence interval (CI), 14.7 to 18.5; p<0.0001) and the ranibizumab 0.5 mg group by 18.3 ± 13.2 letters (95% CI, 16.0 to 20.6; p<0.0001) compared to placebo (7.3 ± 13 letters; 95% CI, 5.1 to 9.5). A significantly higher proportion of patients in the ranibizumab 0.3 mg (20.1%; p<0.005) and 0.5 mg (14.5%; p<0.005) groups achieved a gain of at least 15 letters in BCVA compared to placebo (3.8%) by day 7. These significant differences continued through 6 months of treatment (ranibizumab 0.3 mg, 55.2%, p<0.0001 vs placebo; ranibizumab 0.5 mg, 61.1%, p<0.0001 vs placebo; placebo, 28.8%). Significantly more patients in the ranibizumab 0.3 mg (67.9%) and 0.5 mg (64.9%) groups achieved a Snellen equivalent BCVA of at least 20/40 compared with 41.7% of patients in the placebo group (p<0.0001 for each ranibizumab group vs placebo) at month 6. Rescue grid laser treatment was required by significantly more patients in the placebo group (54.5%) compared with the ranibizumab 0.3 mg (18.7%) and 0.5 mg (19.8%) groups.

In Study RVO-2, patients with macular edema following central RVO received monthly ranibizumab 0.3 mg (n=132), ranibizumab 0.5 mg (n=130), or placebo (n=130) injections for 6 months. Monthly injections could be continued during the observation period (6 to 12 months) if pre-specified criteria were met. At baseline, mean BCVA was 48.3 letters (range, 9 to 73). After 6 months, BCVA significantly improved in both the ranibizumab 0.3 mg group by 12.7 ±15.9 letters (95% confidence interval (CI), 9.9 to 15.4; p<0.0001) and the ranibizumab 0.5 mg group by 14.9 ±
13.2 letters (95% CI, 12.6 to 17.2; p<0.0001) compared to placebo (0.8 ± 16.2 letters; 95% CI, -2 to 3.6). A significantly higher proportion of patients in the ranibizumab 0.3 mg (22%; p<0.0001) and 0.5 mg (26.9%; p<0.0001) groups achieved a gain of at least 15 letters in BCVA compared to placebo (3.8%) by day 7. These significant differences continued through 6 months of treatment (ranibizumab 0.3 mg, 46.2%, p<0.0001 vs placebo; ranibizumab 0.5 mg, 47.7%, p<0.0001 vs placebo; placebo, 16.9%). Significantly more patients in the ranibizumab 0.3 mg (43.9%) and 0.5 mg (46.9%) groups achieved a Snellen equivalent BCVA of at least 20/40 compared with 20.8% of patients in the placebo group (p<0.0001 for each ranibizumab group vs placebo) at month 6.

The efficacy and safety of intravitreal bevacizumab injections into eyes with macular edema secondary to central retinal vein occlusion (CRVO) was evaluated in a prospective clinical trial (n=45 eyes) by Zhang et al.21 Study subjects were treated with 3 initial intravitreal bevacizumab injections of 1.25 mg at monthly intervals. Retreatment was based on central retinal thickness (CRT) measured by optical coherence tomography (OCT) performed monthly, while fluorescein angiography was performed every 3 months. Main outcome parameters were visual acuity (VA, using the Early Treatment of Diabetic Retinopathy Study protocol) and CRT in an 18-month follow-up period. Mean VA increased from 40.9 letters at baseline to 61.9 letters (+21 letters; p<0.001) at month 18; CRT decreased from 572.3 μm at baseline to 273.2 μm at month 18 (-299.1 μm; p<0.001). Neither age, duration of CRVO, baseline VA, nor baseline CRT was correlated with the change in VA. No drug-related systemic or ocular side effects were observed following intravitreal bevacizumab treatment.

The efficacy of intravitreal bevacizumab as the primary treatment of macular edema due to retinal vein occlusions was evaluated by Figueroa et al. in a study of patients diagnosed as having central retinal vein occlusion (CRVO) (n=18 eyes) or branch retinal vein occlusion (BRVO) (n=28 eyes) with visual acuity of less than 20/40 and macular edema (>300 microm central retinal thickness).22 After an initial intravitreal injection of bevacizumab, re-treatment was performed if intraretinal or subretinal fluid with distortion of the foveal depression was found in optical coherence tomography. During a 6-month period, the mean number of injections per patient was 3.7 (BRVO group) and 4.6 (CRVO group). In the BRVO group, mean baseline logMAR visual acuity was 0.80 (SD 0.38) and macular thickness was 486.9 microm (SD 138.5 microm). After 6 months, mean logMAR visual acuity improved significantly to 0.44 (SD 0.34), p<0.001. Mean macular thickness decreased significantly to 268.2 microm (SD 62.5 microm), p<0.001. In the CRVO group, mean baseline logMAR visual acuity was 1.13 (SD 0.21) and macular thickness was 536.4 microm (SD 107.1 microm). Mean final logMAR visual acuity improved significantly to 0.83 (SD 0.45), p<0.001. Mean macular thickness decreased significantly to 326.17 microm (SD 96.70 microm), p<0.001. The investigators concluded that intravitreal bevacizumab is an effective primary treatment option for macular edema due to retinal occlusions. However, multiple injections are necessary to maintain visual and anatomic improvements.

Hoeh et al. enrolled patients (n=61) with persistent macular edema (ME) (>250 μm) due to central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) in a study to evaluate the long-term outcome of an optical coherence tomography (OCT)-guided reinjection scheme for bevacizumab treatment of their ME.23 Visual acuity (ETDRS), ophthalmic examination and OCT were performed at baseline and at 6- to 8- week intervals. Patients received intravitreal bevacizumab 2.5 mg/0.1 ml, with re-injections only performed if OCT showed persistent or recurrent ME. Minimum follow-up was 25 weeks, while mean follow-up was 60±29 wks. In CRVO patients (n=27), central retinal thickness (CRT) decreased from 748 ± 265 μm to 372 ± 224 μm (p<0.001) and visual acuity (VA) improved by 1.9 ± 3.2 lines. In BRVO patients (n=34), mean CRT decreased from 601±206 μm to 386±178 μm (p<0.001) and VA improved by 1.8±2.6 lines. Thirty-three percent of CRVO and 15% of BRVO patients did not show a ME recurrence for ≥25 wks at last visit. Thirty-seven percent of CRVO and 50% of BRVO patients suffered recurrences of ME within the last 25 wks, whereas 30% of CRVO and 35% of BRVO patients did not achieve a complete resolution of ME at any follow-up visit after receiving a minimum of three injections. In CRVO and BRVO, final VA was correlated significantly with initial VA, patients’ age and final
CRT. The researchers concluded that patients with RVO benefit from treatment with bevacizumab.

Twenty-nine consecutive eyes with macular edema secondary to BRVO (21 eyes) or CRVO (8 eyes) were included in a prospective clinical trial by Prager et al.24 Eyes were treated with three initial intravitreal bevacizumab injections of 1 mg at a monthly interval. Retreatment was based on central retinal thickness (CRT) based on optical coherence tomography. If continuous injections were indicated up to month 6, the dose was increased to 2.5 mg. After 12 months of follow-up, mean visual acuity increased from 50 letters (20/100) at baseline to 66 letters (20/50+1; +16 letters; p<0.001) at month 12 and CRT decreased from 558 µm at baseline to 309 µm at month 12 (-249 µm; p<0.001). Patients received a mean of eight out of 13 possible injections. No drug-related systemic or ocular side effects were observed. Fluorescein angiography revealed no progression of avascular areas. Intravitreal therapy using bevacizumab appears to be a safe and effective treatment in patients with macular edema secondary to retinal vein occlusion. However, the main limitations of this treatment modality are its short-term effectiveness and high recurrence rate.

**Proliferative Diabetic Retinopathy**

Intravitreal bevacizumab has been studied as an adjunct to laser photocoagulation, to facilitate pars plana vitrectomy, and as a monotherapy for treatment of proliferating diabetic retinopathy (PDR).25,67-8,76-7

Ahmadieh et al. evaluated the effect of preoperative intravitreal bevacizumab (IVB) injections on the rate of early (≤4 weeks) postvitrectomy hemorrhage in patients (n=68) with proliferative diabetic retinopathy.26 Subjects were randomly assigned to receive either 1.25 mg IVB (n=35) one week prior to surgery or control (n=33). The primary outcome measure was the incidence of early postvitrectomy hemorrhage. Secondary outcome measures included changes in best-corrected visual acuity (BCVA) and IVB-related adverse events. In the intention-to-treat analysis, the incidence of postvitrectomy hemorrhage 1 week and 1 month after surgery was significantly lower in the IVB group compared with the control group (p=0.023 and p=0.001, respectively). Mean BCVA improved from 1.88 logarithm of minimum angle of resolution (logMAR) units in both study groups before surgery to 0.91 logMAR units and 1.46 logMAR units 1 month after vitrectomy in the IVB and control groups, respectively (p=0.001). Resolution of vitreous hemorrhage was observed in 9 eyes (25.7%) after IVB injection, obviating the need for vitrectomy; the corresponding figure was 2 eyes (6.1%) in the control group (p=0.028). The per-protocol analysis included 16 eyes in the IVB group and 18 eyes in the control group; postvitrectomy hemorrhage occurred less frequently 1 week and 1 month after surgery in the IVB group compared with the control group (p=0.033 and p=0.003, respectively). Mean improvement in BCVA 1 month after vitrectomy was -1.05 logMAR units in the IVB group and -0.42 logMAR units in the control group (p=0.004). No IVB-related complication was observed in the treatment group. The investigators concluded that IVB one week before vitrectomy appears to reduce the incidence of early postvitrectomy hemorrhage in diabetic patients. The need for vitrectomy may be decreased significantly in these cases as well.

In order to evaluate the safety and effectiveness of intravitreal bevacizumab (IVB) as an adjunct to vitrectomy, di Lauro et al. performed a randomized controlled trial on 72 eyes of 68 patients affected by vitreous hemorrhage (VH) and tractional retinal detachment (TRD) which occurred as a consequence of active proliferative diabetic retinopathy (PDR).27 Participants were assigned in a 1:1:1 ratio to receive a placebo injection or an intravitreal injection of 1.25 mg of bevacizumab, either 7 or 20 days before the vitrectomy. Complete ophthalmic examinations and color fundus photography were performed at baseline and 1, 6, 12, and 24 weeks after the surgery. In the placebo group, intraoperative bleeding occurred in 19 cases (79.1%), the use of endodiathermy was necessary in 13 patients (54.1%), relaxing retinotomy was performed on one patient (4.1%), and in four cases (16.6%) iatrogenic retinal breaks occurred. The surgical mean time was 84 minutes (SD 12 minutes). In subjects receiving IVB seven days prior to vitrectomy, intraoperative bleeding occurred in two cases (8.3%) and the use of endodiathermy was necessary in two
patients (8.3%). No iatrogenic breaks occurred during the surgery. The surgical mean time was 65 minutes (SD 18 minutes). For those subjects receiving IVB twenty days before vitrectomy, intraoperative bleeding occurred in three cases (12.5%), the use of endodiathermy was necessary in three patients (1.5%), and an iatrogenic break occurred in one patient (4.1%) while the delamination of fibrovascular tissue was being performed. The surgical mean time was 69 minutes (SD 21 minutes). The average difference in the surgical time was statistically significant between the placebo group and the 7-day IVB group (p=0.025), and between the placebo group and the 20-day IVB group (p=0.031). At completion of surgery, the retina was completely attached in all eyes. The researchers concluded that best surgical results are achieved performing the IVB 7 days preoperatively.

Moradian et al. published an analysis of the efficacy of IVB in 38 eyes with active progressive PDR.28 Patients had either vascularized fibrovascular tissue refractory to PRP or vitreous hemorrhage precluding PRP. Patients were treated with 1, 2, or 3 IVB injections at 6 to 12 week intervals at the physician’s discretion. At 20 weeks, best corrected visual acuity had improved by 0.63 ± 0.35 logMAR (p=0.002), and the number of patients with no vitreous hemorrhage had increased from 6 to 28 patients (p=0.002). Two of 12 patients who received 2 IVB injections developed tractional retinal detachment that necessitated PPV surgery.

Neovascular Glaucoma
Ghosh et al. present the outcome of concomitant treatment with diode laser cyclophotocoagulation (CPC) and intravitreal bevacizumab (IVB) in painful eyes with poor visual potential in a case series of consecutively diagnosed neovascular glaucoma (NVG).29 Twelve patients (14 eyes) were treated with CPC and concurrent IVB 0.05 mL (1.25 mg). Study endpoints were lowering of intraocular pressure (IOP), regression of anterior segment neovascularization, and resolution of pain. The mean preoperative IOP was 42.1 ± 11.4 and was lowered to 16.6 ± 7.1 mmHg at 1-month post-CPC. Anterior segment neovascularization regressed dramatically within 1 week of IVB in 12 eyes. Thirteen eyes reported persistent relief of ocular pain at 6 months following treatment. The authors concluded that combined IVB and CPC treatment for NVG provides rapid control of anterior segment neovascularization and may lead to improved symptomatic relief and IOP control.

To evaluate the effect of intravitreal bevacizumab injection in cases of neovascular glaucoma, Ghanem et al. studied 16 eyes of 16 patients with rubeosis iridis and secondary glaucoma.30 Patients were administered an intravitreal injection of bevacizumab (2.5 mg) and were followed for 2 months. Partial or complete regression of iris neovascularization was noted 1 week after injection of bevacizumab. Reproliferation of new vessels was detected in 25% of the cases after 2 months. The mean intraocular pressure (IOP) before injection was 28 ± 9.3 mm Hg under topical β-blocker and systemic acetazolamide. One week after injection, the IOP decreased to 21.7 ± 11.5 mm Hg (5 cases without anti-glaucoma drugs, 6 cases with topical β-blocker and 5 cases with both topical β-blocker and systemic acetazolamide). The authors concluded that intravitreal bevacizumab injection leads to regression of iris neovascularization with subsequent drop of IOP in eyes with neovascular glaucoma.

Moraczewski et al. report a retrospective, non-comparative, consecutive, interventional case series of the treatment of neovascular glaucoma with intravitreal bevacizumab in 56 eyes at the University of Miami, Florida, Bascom Palmer Eye Institute.31 The authors’ impression both clinically and from a review of available literature is that early diagnosis and treatment of NVG with intravitreal bevacizumab may lead to improved outcomes. If bevacizumab is administered when the anterior chamber angle is open at the time of NVG diagnosis, it is postulated that IOP may be controlled without the need for surgical procedures. This study underscores the concept that, if followed long enough, the majority of patients regardless of initial angle status and initial IOP lowering, will require surgical intervention for the control of IOP. The cumulative proportion of eyes requiring a second injection of bevacizumab increases linearly with time and is related to recurrent or persistent iris neovascularization or angle neovascularization. Bevacizumab induced
regression of neovascularization is often temporary and recurrence is possible, while panretinal photocoagulation provides a more permanent reduction of the ischemic angiogenic stimulus. At this institution, treatment of NVG with intravitreal bevacizumab is the standard of care, including: 1) Administering intravitreal bevacizumab at the time of diagnosis of NVG; 2) Administering panretinal photocoagulation shortly thereafter, and; 3) lowering IOP medically and via placement of a drainage device if necessary.

Wakabayashi et al. evaluated 41 eyes in 30 patients with iris neovascularization (INV) or neovascular glaucoma (NVG) secondary to ischemic retinal disorders. Patients received 1mg intravitreal injection of bevacizumab and were followed for 6 months. In the 9 eyes with INV, neovascularization regressed or resolved after 1 injection, but recurred in 4 eyes by 6 months requiring additional treatment. In the 17 eyes with open-angle NVG, rapid neovascular regression with IOP normalization occurred in 12 eyes within 1 week after injection. The remaining 5 eyes required surgery by 6 months follow-up, despite repeated intravitreal bevacizumab injections. In the 15 eyes with closed-angle NVG, neovascularization resolved but intravitreal bevacizumab failed to control IOP. Fourteen of the 15 eyes required surgery by 2 months after initial injection. The authors conclude that intravitreal bevacizumab is well tolerated and apparently effective in stabilizing neovascularization in INV and controlling IOP in early open-angle NVG. In advanced NVG with angle closure, intravitreal bevacizumab cannot control IOP but may play a role in adjunctive therapy to improve subsequent surgical results. Further evaluation in controlled randomized studies is warranted.

Costagliola et al. conducted a prospective study of 26 eyes from 23 patients to examine the potential efficacy and safety of intravitreal injection of bevacizumab (IVB) in the treatment of NVG in patients who had already undergone the standard retinal ablative procedure. Clinical data including diagnosis, visual acuity, iris fluorescein angiography stage and intraocular pressure (IOP), were collected. Three injections of bevacizumab were scheduled for each recruited eye at 4-week intervals. All investigations were repeated the day before the IVB (1.25 mg/0.05 ml) and at the 1-, 3-, 6-, 9- and 12-month follow-up. Regression of corneal edema together with significant pain reduction was achieved in all eyes after the first IVB, without any noteworthy improvement of visual acuity. At the end of the scheduled protocol (three IVB injections), regression of iris neovascularization was documented in all patients, together with significant improvement of visual acuity. The IOP reduction from baseline ranged from 30 to 0 mmHg (12.1±8 mmHg). Intravitreal bevacizumab, as adjunctive treatment to the standard retinal ablative procedure, seems promising for the management of conditions responsible of retinal ischemia/hypoxia associated with NVG.

Ehlers et al. report a retrospective, consecutive case-control study of patients receiving same-day combination intravitreal bevacizumab/panretinal photocoagulation (PRP) for the treatment of neovascular glaucoma (NVG) compared with PRP alone. Visual acuity, intraocular pressure (IOP), presence of anterior segment neovascularization, and required glaucoma interventional procedures were recorded. A total of 23 patients were identified, 11 in the bevacizumab/PRP group and 12 in the PRP alone group. The bevacizumab/PRP group had a significant reduction in IOP compared with the PRP alone group (-11 vs. 0 mmHg, respectively; p=0.03). There was a significantly higher frequency and rate of neovascular regression in the combination therapy group than in the PRP only group (11 vs 2 eyes [p<0.001] and 12 vs 127 days [p<0.0001], respectively). Average follow-up was 143 days for the bevacizumab/PRP group and 118 days for the PRP alone group. The authors found that combination treatment resulted in more rapid decrease in IOP. In addition, the combination group had increased frequency and rapidity of regression of neovascularization. This study provides a foundation for further research and suggests consideration for a possible new paradigm for the treatment of NVG.

**Choroidal Neovascularization**

**Choroidal neovascularization secondary to pathologic myopia:**

Hayashi et al. conducted an open-label, consecutive, interventional case series to determine the 2-year results of intravitreal bevacizumab in highly myopic eyes with choroidal neovascularization.
Seventy-five eyes of 69 consecutive Japanese patients with either subfoveal or nonsubfoveal myopic CNVs were studied. The eyes were treated with intravitreal bevacizumab and followed for at least 2 years. The best-corrected visual acuities at the baseline in eyes with subfoveal CNV were compared with that in eyes with nonsubfoveal CNV at 2 years after the intravitreal bevacizumab. Although the difference in eyes with a subfoveal CNV was not significant, the mean best-corrected visual acuity in eyes with nonsubfoveal CNV was significantly improved from 0.53 ± 0.36 logarithm of the minimal angle of resolution units (Snellen 20/66) before intravitreal bevacizumab to 0.29 ± 0.36 logMAR units (Snellen 20/40) (p<0.001) two years after intravitreal bevacizumab. The incidence of chorioretinal atrophy after 2 years was 3 of 49 (6.1%) in eyes with nonsubfoveal CNV and 21 of 26 (80.8%) in eyes with subfoveal CNV (p<0.001). Furthermore, the chorioretinal atrophy area with nonsubfoveal CNV was 0.05 ± 0.21 mm, which was also significantly smaller than that of subfoveal CNV at 1.76 ± 1.60 mm (p<0.001). The investigators concluded that intravitreal bevacizumab is a good treatment for eyes with nonsubfoveal CNV; however, another treatment is necessary for eyes with a subfoveally located CNV.

Yoon et al. compared visual outcomes after treatment with intravitreal antivascular endothelial growth factor (anti-VEGF) injection or photodynamic therapy (PDT) in patients with myopic choroidal (CNV).36 One hundred and forty-two eyes of 128 consecutive patients treated with anti-VEGF (ranibizumab or bevacizumab) and/or PDT for myopic choroidal neovascularization were retrospectively reviewed. Patients were categorized into 3 groups: PDT (51 eyes), anti-VEGF (63 eyes), and a combination group (PDT with anti-VEGF) (28 eyes). Corrected visual acuity values at baseline and 3, 6, 9, and 12 months after treatment were compared. The anti-VEGF group showed significant postoperative improvement in visual acuity compared with the PDT and combination groups (p=0.01 and 0.04, respectively). The anti-VEGF group demonstrated visual improvement from baseline at every follow-up visit after treatment (p=0.04, 0.02, 0.01, and 0.002, respectively). The anti-VEGF group showed visual improvement (Snellen equivalent) from 0.57 logarithm of the minimum angle of resolution (logMAR) at 0.27 to 0.33 logMAR at 0.47 (p=0.01). Furthermore, 98.4% of patients in the anti-VEGF group and 92.8% of those in the combination group lost <15 letters from baseline visual acuity compared with 72.6% in the PDT group (p=0.001 and 0.02, respectively). In the anti-VEGF group, 39.7% of patients improved from baseline by 15 or more letters compared with 17.7% in the PDT group (p=0.02) and 21.4% in the combination group (p=0.07). Based on these findings, the investigators concluded that intravitreal anti-VEGF injection is superior to PDT alone or a combination of PDT with anti-VEGF for treating myopic choroidal neovascularization.

Vadalà et al. assessed the efficacy and safety of ranibizumab in the treatment of choroidal neovascularisation (CNV) caused by pathologic myopia (PM) in a prospective, multicentre, interventional case series.37 Forty eyes of 39 consecutive patients with PM and CNV were treated with ‘on demand’ intravitreal injection of ranibizumab 0.5 mg. Final best corrected visual acuity (BCVA) and its change from baseline were the main outcome measures. Median follow-up was 13.3 ± 2 (range 12-18) months. Fifteen eyes (37.5%) had previously been treated with photodynamic therapy (PDT). The mean baseline logarithm of the minimum angle of resolution (logMAR) BCVA was 0.68 ± 0.34 (Snellen equivalent 20/131) and 21 ± 16 letters. The final mean logMAR BCVA was 0.27 ± 0.2 (p=0.008) (20/42) and 40.5 ± 14 letters (p=0.01). Mean final VA improved in 82.5% of patients, in 60% by 3 or more lines (median number of lines gained 2.9). Age and previous PDT did not influence the results (p>0.05). The mean number of injections was 2.8 ± 1.2 (range 1-6). No ocular or systemic side effects were observed. Ranibizumab was an effective treatment for stabilizing and improving vision with a low number of injections in 92.5% of patients with myopic CNV in a long-term follow-up.

In a prospective, multicenter, consecutive, nonrandomized, interventional case series, Silva et al. evaluated the safety and efficacy of intravitreal ranibizumab in the treatment of choroidal neovascularization secondary to pathologic myopia.38 The study included 34 eyes of 32 patients; 13 eyes had previous photodynamic therapy, and 21 eyes had no previous treatment. The
patients were followed for ≥12 months, with best-corrected visual acuity, optical coherence tomography, and the presence of metamorphopsia assessed monthly. Mean visual acuity improved 8 letters from baseline to 12-month follow-up, and the difference was statistically significant (p<0.001): 100% of the eyes lost <3 lines on the Early Treatment Diabetic Retinopathy Study chart, 24% of the eyes improved ≥3 lines, 44% improved ≥2 lines, 65% improved ≥1 line, and 79% improved ≥0 lines. Central retinal thickness decreased significantly from baseline to the 12-month follow-up (p<0.01). A mean of 3.6 treatments were performed during the 12-month follow-up, and no systemic or ocular side effects were registered during that time.

Choroidal neovascularization secondary to angioid streaks/pseudoxanthoma elasticum: Finger et al. investigated the long-term effectiveness of intravitreal bevacizumab for treating active choroidal neovascularizations in pseudoxanthoma elasticum (PXE).39 Fourteen patients (16 eyes) received intravitreal bevacizumab (1.5 mg), were evaluated monthly, and received further treatments depending on disease activity. Examinations included best-corrected visual acuity, biomicroscopy, optical coherence tomography, fluorescein angiography and indocyanine green angiography, fundus autofluorescence, and digital fundus photography. Areas of atrophy of the retinal pigment epithelium and retinal fibrosis were quantified using semiautomated detection on fundus autofluorescence images. Mean age of the cohort was 55 ± 13 years, and mean best-corrected visual acuity at baseline was 20/80 (logarithm of the minimum angle of resolution, 0.56, SD, 0.51). At last follow-up, after an average of 6.5 ± 5.7 injections over 28 months, best-corrected visual acuity was 20/40 (logarithm of the minimum angle of resolution, 0.31, SD, 0.32; p=0.04). Central retinal thickness was reduced from 254 ± 45 μm to 214 ± 40 μm (p=0.035). The size of retinal pigment epithelial atrophy and retinal fibrosis measured on fundus autofluorescence images increased in both the treated eye and the fellow eye (p<0.05). Best-corrected visual acuity of patients with early disease compared with that of those with advanced disease improved significantly more over the treatment course (20/25 vs. 20/63; p=0.008). The authors reported that intravitreal bevacizumab therapy demonstrates long-term effectiveness by preserving function in advanced disease and improving function in early disease. Best results of treating active choroidal neovascularizations in PXE are achieved when treatment starts as early in the disease as possible.

El Matri et al. evaluated the efficacy and safety of intravitreal bevacizumab for the treatment of choroidal neovascularization associated with angioid streaks in a retrospective case series of eighteen eyes of 17 patients treated between October 2006 and May 2008.40 Ophthalmic evaluation, including best corrected visual acuity (BCVA), slit lamp biomicroscopic examination, optical coherence tomography (OCT) and fluorescein angiography, was performed before and after treatment. Retreatment was allowed every 4–6 weeks in case of persistent symptoms or CNV activity on OCT. Main outcome measures were changes in BCVA and central retinal thickness on OCT. The mean number of injections was 4.8 at one year. Twelve eyes (66.6%) received five injections or more. The mean BCVA at baseline was 20/60 (range 20/400 to 20/32) and improved to 20/44 (range 20/160 to 20/20) at 1 year (p=0.014). The BCVA improved by three or more lines in eleven eyes (61.11%) and remained within two lines of baseline in seven eyes (38.8%). Mean central retinal thickness was 404.2 μm (range 160–602 μm) at baseline and decreased to 300.5 μm (range 150–523 μm) at 1 year (p=0.022). No ocular or systemic complications were noted. The 1-year outcomes suggest intravitreal bevacizumab to be a promising treatment for CNV associated with angioid streaks, resulting in both functional and anatomical improvements. Repeated injections are needed to maintain these results. Further long term studies are required to confirm these findings.

Mimoun et al. retrospectively analyzed the efficacy of intravitreal ranibizumab injections for the management of choroidal neovascularization (CNV) in patients with angioid streaks.41 In a nonrandomized, double-center, retrospective, interventional case series, patients were treated with intravitreal ranibizumab injections (0.5 mg/0.05 mL). The primary end point was the percentage of eyes with stable or improved visual acuity at the end of follow-up. Secondary end points were the percentage of eyes with stable or decreased macular thickness on optical coherence tomography and the percentage of eyes with persistent leakage on fluorescein angiography.
angiography at the last follow-up examination. Thirty-five eyes of 27 patients were treated with repeated intravitreal ranibizumab injections (mean, 5.7 injections; range, 2 to 14 injections) for a mean of 24.1 months (range, 6 to 37 months). At the end of follow-up, visual acuity was stabilized or improved in 30 (85.7%) of 35 eyes. Macular thickness had stabilized or decreased in 18 (51.5%) of 35 eyes. At the last follow-up examination, on fluorescein angiography, no further leakage was observed in 23 (65.7%) of 35 eyes.

Myung et al. reported long-term results of intravitreal antivascular endothelial growth factor therapy in the management of choroidal neovascularization in patients with angioid streaks associated with pseudoxanthoma elasticum.42 Nine eyes of nine consecutive patients were managed with either bevacizumab 1.25 mg/0.05 mL or ranibizumab 0.5 mg/0.05 mL. The main outcome measures were visual acuity and greatest lesion height as measured by optical coherence tomography. During the mean follow-up period of 28.6 months, eyes received an average of 8.4 injections. At baseline, the mean visual acuity was 20/368 (median, 20/60) and improved to 20/281 (median, 20/40) at the last visit (p=0.14). Visual acuity either improved or stabilized in all 9 eyes (100%). Serial optical coherence tomography measurements showed a mean of 353 mum at baseline and decreased to 146 mum at the last visit (p= 0.005). No complications were noted. These long-term results support the use of intravitreal antivascular endothelial growth factor therapy for the management of choroidal neovascularization in patients with pseudoxanthoma elasticum.

**Choroidal neovascularization secondary to ocular histoplasmosis syndrome (OHS):**

Cionni et al. conducted a retrospective, comparative case series of 150 eyes in 140 patients treated with intravitreal bevacizumab (IVB) for choroidal neovascularization (CNV) secondary to presumed ocular histoplasmosis syndrome (POHS).43 Subjects received either IVB monotherapy (n=117 eyes) or combination IVB and verteporfin photodynamic therapy (IVB/PDT) (n=34 eyes). Visual acuity (VA) at 12 and 24 months was analyzed. Secondary outcome measures included the number of injections per year and treatment-free intervals. For all patients, the average pretreatment logarithm of minimum angle of resolution (logMAR) was 0.63 (Snellen equivalent 20/86) with a 12-month logMAR VA of 0.45 (Snellen equivalent 20/56) and a 24-month logMAR VA of 0.44 (Snellen equivalent 20/55). The mean follow-up was 21.1 months with an average of 4.24 IVB injections per year. There was no significant difference in initial VA, VA at 12 months, VA at 24 months, or number of eyes with a 3-line gain between the IVB monotherapy and IVB/PDT groups. Thirty-eight percent (39/104) of eyes gained 3 lines or more, and 81.2% (84/104) of subjects had maintained or improved their starting VA at 1 year. The proportion of subjects maintaining a 3-line gain in VA was relatively preserved at 2 years (29.8%, 17/57) and 3 years (30.3%, 10/32) follow-up. There was no increase in the proportion of subjects losing 3 lines or more over 3 years of follow-up. The authors concluded that there is no significant difference in VA outcomes between IVB monotherapy versus IVB/PDT combination therapy. The use of IVB alone or in combination with PDT results in significant visual stabilization in the majority of patients with CNV secondary to POHS.

Shadlu et al. conducted a retrospective chart review of 28 eyes of 28 patients who underwent intravitreal administration of bevacizumab for treatment of choroidal neovascularization secondary to OHS.44 The mean follow-up period was 22.43 weeks with patients receiving an average of 1.8 intravitreal injections. The investigators found that the treatment was of benefit to improve or stabilize the visual acuity in a significant majority (24 eyes, 85.7%) of patients with neovascular complications of OHS.

In a retrospective chart review of 54 eyes, Nielsen et al. studied the effect of treatment with intravitreal anti-VEGF therapy for choroidal neovascularization in ocular histoplasmosis syndrome.45 Either bevacizumab or ranibizumab were administered on an average of 4.5 injections per patient per year of follow-up. Mean visual acuity improved from 20/53 to 20/26 over an average of 26.8 months. Vision loss was seen in only three eyes with loss limited to a single line of vision. Patients experienced no serious complications from treatment. Long-term
intravitreal anti-VEGF therapy with bevacizumab or ranibizumab is beneficial in treatment of choroidal neovascularization in ocular histoplasmosis syndrome.

There are additional small published studies and reports that provide support for the use of both bevacizumab and ranibizumab to treat choroidal neovascularization secondary to pathologic myopia, angioid streaks/pseudoxanthoma elasticum, or ocular histoplasmosis syndrome (OHS).46-60

**Unproven Use:**

**Retinopathy of Prematurity**

Because VEGF is involved in a wide variety of physiologic processes, the ocular and systemic safety of anti-VEGF agents is of prime concern in neonates. In a review by Haigh, the role of in vivo VEGF-signaling during the development of early cardiovascular and other organ systems is discussed.61 Differential VEGF isoform expression controls developmental angiogenesis. The VEGF-mediated assembly of a functional vasculature is a prerequisite for the proper formation of other organs and for tissue homeostasis.

Mintz-Hittner et al. conducted a prospective, controlled, randomized, stratified, multicenter trial to assess intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3+ retinopathy of prematurity (ROP).62 Of the 150 infants (300 eyes) enrolled in the study, 143 survived to 54 weeks and were included in the primary outcome analysis. Participants were randomly assigned to receive bilateral treatment with either 0.625 mg intravitreal bevacizumab (n=70) or conventional laser (n=73) therapy. The primary outcome measure was recurrence of ROP in one or both eyes requiring retreatment before 54 weeks’ age. Retinopathy of prematurity recurred in 4 infants in the bevacizumab group (6 of 140 eyes [4%]) and 19 infants in the laser-therapy group (32 of 146 eyes [22%], p=0.002). A significant treatment effect was found for zone I retinopathy of prematurity (p=0.003) but not for zone II disease (p=0.27). Despite the observed efficacy of bevacizumab in this trial, the authors stated that their study was too small to determine whether bevacizumab was safe in this clinical setting. They acknowledge that safety is the primary reason for exercising caution when considering the use of intravitreal bevacizumab in the treatment of neonates. Both morbidity and mortality must be considered.

Knowing the key role vascular endothelial growth factor (VEGF) plays in normal angiogenesis and neuroprotection, Hard and Hellstrom conducted a literature search to review studies on safety, pharmacokinetics, and dosage of bevacizumab in relation to the developmental stages of critical organs during the third trimester and early postnatal life.63 Based upon their review, the authors suspect that serum bevacizumab levels 8 weeks after intravitreal administration prevent VEGF from acting in preterm infants at a developmental stage when VEGF is essential. The authors concluded by suggesting that infants who can be treated successfully with laser should not receive anti-VEGF therapy until controlled pharmacokinetic, dose, efficacy, and safety trials with close monitoring of serum concentrations of VEGF can be conducted.

Sato et al. reported a case series of infants with vascularly active ROP to determine the serum concentrations of bevacizumab and vascular endothelial growth factor (VEGF) in infants (n=11) who received intravitreal bevacizumab and to determine whether the changes in the serum concentration of bevacizumab were significantly correlated with the serum concentration of VEGF after intravitreal bevacizumab.64 Subjects received 0.25 mg or 0.5 mg of intravitreal bevacizumab to either 1 eye (unilateral cases) or both eyes (bilateral cases). The serum concentration of bevacizumab before and 1 day, 1 week, and 2 weeks after a total of 0.5 mg of intravitreal bevacizumab was 0 ng/mL, 195 ± 324 ng/mL, 946 ± 680 ng/mL, and 1214 ± 351 ng/mL, respectively. The serum bevacizumab level before and 1 day and 1 week after a total 1.0 mg of intravitreal bevacizumab was 0 ng/mL, 248 ± 174 ng/mL, and 548 ± 89 ng/mL, respectively. The serum concentration of VEGF before and 1 day, 1 week, and 2 weeks after a total of 0.5 mg intravitreal bevacizumab was 1628 ± 929 pg/mL, 427 ± 140 pg/mL, 246 ± 110 pg/mL, and 269 ± 157 pg/mL, respectively. There was a significant negative correlation (r=-0.575, p=0.0125) between the serum concentration of bevacizumab and VEGF when a total of 0.25 mg or 0.5 mg
of bevacizumab was injected. These results indicate that bevacizumab can escape from the eye into the systemic circulation and reduce the serum level of VEGF in infants with ROP. Continued extensive evaluations of infants are warranted for possible effects after intravitreal bevacizumab in ROP patients.

Micieli et al. conducted a systematic literature review of trials reporting the use of bevacizumab in ROP. Their findings included nine articles comprised of six case reports, two retrospective studies, and one prospective case series representing 77 eyes of 48 infants. Bevacizumab doses ranged from 0.4 to 1.25 mg, with 0.75 mg being the most common. One retrospective study and the prospective case series used bevacizumab alone, whereas the other retrospective study used bevacizumab before and with retinal surgery. The lack of high-quality studies prevents any strong conclusions regarding the efficacy of bevacizumab for ROP. Further randomized control trials are warranted and should aim to assess statistically the optimal timing, frequency, and dose of the drug. Careful attention should be given to the potential for systemic complications and long-term effects of intravitreal bevacizumab in infants.

Technology Assessments
Hayes has compiled a Medical Technology Directory on the use of bevacizumab (Avastin®) for Age-Related Macular Degeneration, dated September 29, 2008. The Directory determines that currently available evidence is insufficient to conclude that bevacizumab improves clinical outcomes in patients with age-related macular degeneration (AMD), assigning a Hayes Rating C (potential but unproven benefit). Specific patient selection criteria remain to be defined, and long-term safety data are not yet available. It is not clear whether bevacizumab is at least as effective as other Food and Drug Administration (FDA)-approved biologics. Updated Search Summaries published on September 27, 2011 and on September 10, 2012 resulted in no changes to the Hayes rating established in the original publication.

Professional Societies
In December 2011, the Royal College of Ophthalmologists released a scientific statement on bevacizumab use in medical ophthalmology. A working group of the Scientific Committee of the College considered the published literature relating to the efficacy and safety of bevacizumab (Avastin) and ranibizumab (Lucentis) in the treatment of the neovascular form of age-related macular degeneration (AMD). The College view is that the current published literature is consistent with the conclusion that bevacizumab and ranibizumab are equally effective in the treatment of neovascular age-related macular degeneration and there is no convincing evidence of a clinically significant difference in the incidence of serious adverse events between the two groups.

According to the American Society of Retina Specialists (ASRS), bevacizumab is being used by a large number of retinal specialists who believe that it is reasonable and medically necessary for the treatment of some patients with macular edema and abnormal retinal and iris neovascularization.

The American Academy of Ophthalmology (AAO) supports the use of bevacizumab, pegaptanib, and ranibizumab for treatment of age-related macular degeneration as a recommendation with high importance to clinical care.

In their Diabetic Retinopathy Preferred Practice Pattern, the AAO states that recent data from the Diabetic Retinopathy Clinical Research Network (DRCR.net) suggest that intravitreal antivascular endothelial growth factor agents may play an important role in the treatment of clinically significant macular edema. Adjunctive treatments that may be considered for the treatment of diabetic retinopathy include intravitreal corticosteroids or anti-vascular endothelial growth factor agents.

The AAO released a policy statement on intravitreal injections that states: Patients undergoing intravitreal injections require the care and judgment of medically trained physicians experienced...
in diagnosing and treating retinal diseases as well as potential complications, which may necessitate surgical intervention. The AAO strongly supports the position that all intravitreal injections should be performed only by licensed MDs or DOs specializing in eye treatment.

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

**Avastin (bevacizumab)**
The statements below are for information only. Oncology indications for bevacizumab are listed in the NCCN Drugs & Biologics Compendium.

- Bevacizumab, in combination with intravenous 5-fluorouracil–based chemotherapy, is indicated for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum.74
- Bevacizumab, in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer.74
- Bevacizumab for treatment of glioblastoma, is indicated as a single agent for patients with progressive disease following prior therapy.74
- Bevacizumab, in combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma.74

Administration of bevacizumab infusions or intravitreal injections for the treatment of ophthalmologic conditions is considered off-label.

The FDA issued an alert dated August 30, 2011 that notification had been received from the Florida Department of Health (DOH) regarding a cluster of *Streptococcus endophthalmitis* infections in three clinics following intravitreal injection of repackaged Avastin. Investigators traced the tainted injections to a single pharmacy that had repackaged the Avastin from sterile injectable 100 mg/4 mL, single-use, preservative-free vials into individual 1 mL single-use syringes. The alert reminded health care professionals that repackaging sterile drugs without proper aseptic technique can compromise product sterility, potentially putting the patient at risk for microbial infections. Health care professionals should ensure that drug products are obtained from appropriate, reliable sources and properly administered.

**Eylea (aflibercept)**
Aflibercept is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD) and macular edema following central retinal vein occlusion (CRVO).5

**Lucentis (ranibizumab)**
Ranibizumab is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), and diabetic macular edema.7

**Macugen (pegaptanib)**
Pegaptanib is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD).6

**APPLICABLE CODES**
The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] 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. Coverage is determined by the benefit document.

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J2503 Injection, pegaptanib sodium, 0.3 mg
J2778 Injection, ranibizumab, 0.1 mg
J9035 Injection, bevacizumab, 10 mg

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**ICD-10 Codes (Preview Draft)**

In preparation for the transition from ICD-9 to ICD-10 medical coding on **October 1, 2014**

A sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. *The effective date for ICD-10 code set implementation is subject to change.*

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### REFERENCES


**POLICY HISTORY/REVISION INFORMATION**

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