Medicare Part B
Ocular Angiogenesis Inhibitors
Criteria Through Bevacizumab

For CBC: This program will target all agents except Visodyne. The preferred agent will be Avastin

For RI This program will target Eylea, Lucentis and Beovu. Preferred agents will be Avastin

FDA APPROVED INDICATIONS AND DOSAGE[1-4,13,16]

Agent(s)	Indication(s)	Dosage
Beovu® (brolucizumab-dbll) Injection for intravitreal use	Neovascular (Wet) Age-Related Macular Degeneration (AMD)	6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection monthly (approximately every 25-31 days) for the first three doses, followed by 6 mg (0.05 mL) by intravitreal injection once every 8-12 weeks
Eylea® (afibercept) Injection for intravitreal use	Neovascular (Wet) Age-Related Macular Degeneration (AMD)	2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months) *Although Eylea may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when Eylea was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months)
	Macular Edema following Retinal Vein Occlusion (RVO)	2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly)

Agent(s)	Indication(s)	Dosage
	Diabetic Macular Edema (DME)	2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). *Although Eylea may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when Eylea was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months)
	Diabetic Retinopathy (DR)	2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). *Although Eylea may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when Eylea was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months)
Lucentis® (ranibizumab) Injection for intravitreal use	Neovascular (Wet) Age-Related Macular Degeneration (AMD)	0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days)
	Macular Edema Following Retinal Vein Occlusion (RVO)	0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days)

Agent(s)	Indication(s)	Dosage
	Diabetic Macular Edema (DME)	0.3 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days)
	Diabetic Retinopathy (DR)	0.3 (0.05mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days)
	Myopic Choroidal neovascularization (mCNV)	0.5 (0.05mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days)
Macugen® (pegaptanib) Injection for intravitreal use	Neovascular (Wet) Age-Related Macular Degeneration (AMD)	0.3 mg should be administered once every six weeks by intravitreal injection into the eye to be treated
Susvimo™ (ranibizumab) Injection for intravitreal use via Susvimo ocular implant	The treatment of patients with Neovascular (wet) Age-related Macular Degeneration (AMD) who have previously responded to at least two intravitreal injections of a VEGF inhibitor	**AMD:** 2 mg (0.02 mL of 100 mg/mL solution) continuously delivered via the Susvimo ocular implant with refills administered every 24 weeks (approximately 6 months)
Visudyne® (verteporfin) Injection for intravitreal use	Predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis	6 mg/m body surface area

CLINICAL RATIONALE

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

Age-related macular degeneration (AMD) is the leading cause of severe, irreversible vision impairment in industrialized countries. This degenerative disease affects the central portion of the retina, the macula, resulting in central vision loss. AMD is clinically classified as either dry (atrophic) or wet (neovascular or exudative). Wet AMD is characterized by growth of abnormal vessels into the subretinal space that leak causing collections of subretinal fluid and/or blood beneath the retina. It is estimated that wet AMD only accounts for 10-20% of AMD patients; however, it accounts for 80-90% of patients that suffer severe visual loss or legal blindness. Studies suggest that vascular endothelial growth factor (VEGF) is responsible for iris and retinal neovascularization associated with ischemic retinopathies; subsequently, several isoforms with different binding affinities to the VEGF receptor have been discovered.[6]

Macular Edema Following Retinal Vein Occlusion (RVO)

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder following diabetic retinopathy and is often associated with vision loss. Retinal vein occlusion occurs when there is a partial or complete obstruction of a retinal vein, and it is classified by the location of the occlusion. An RVO involves either a complete or partial decrease in venous outflow within the retinal circulation with varying degrees

of retinal vascular leakage, leading to both macular edema and an increase of intravenous pressure that results in intraretinal hemorrhages. Currently there are no treatments proven to reopen occluded retinal veins; thus, treatments are directed at secondary complications of RVO that affect vision (e.g. macular edema, retinal neovascularization, and anterior segment neovascularization). Anti-VEGF agents are considered first-line therapy for macular edema with intravitreal glucocorticoid therapy and grid laser photocoagulation therapy as distant alternative choices. The anti-VEGF agents are believed to limit macular edema and improve vision by decreasing vascular permeability. Intravitreal glucocorticoids improve visual acuity. However, they may cause cataract formation and moderate/severe increases in intraocular pressure, which is not often caused by the anti-VEGF, making it a less favorable treatment option than anti-VEGF agents.[11]

Diabetic retinopathy (DR) and diabetic Macular Edema (DME)
Diabetic retinopathy is the most common cause of blindness in working-aged adults worldwide. Visual loss from diabetic retinopathy may be secondary to macular edema, which includes retinal thickening and edema of the macula. Other causes may be hemorrhage from new vessels, retinal detachment and neovascular glaucoma. It is believed that chronic hyperglycemia is the main reason for diabetic retinopathy. Diabetic macular edema (DME) is a common cause of visual impairment globally. The underlying progressive retinal microvascular damage is associated with upregulation of VEGF and a multitude of other inflammatory pathways. There is a range of findings, symptoms, and rate of progression in diabetic retinopathy patients necessitating individualistic treatment approaches. Macular edema can occur at any stage of diabetic retinopathy. When macular edema does occur, it manifests itself through retinal thickening and edema of the macula. This can cause associated capillary leakage and if near the macula and not treated can cause loss of visual acuity. Initial treatments options are anti-VEGF agents or laser treatment (focal photocoagulation). Studies have been completed with combination treatment of anti-VEGF and focal photocoagulation suggesting that less frequent treatments are needed as a result. Longer-term studies are still needed to determine the optimal regimen in varying degrees of macular edema. It has been noted that intravitreal triamcinolone injection is an option for macular edema; however, response from treatment in DME is transient and require repeated injections.[7,9]

Myopic Choroidal Neovascularization (CNV)
Myopic choroidal neovascularization (CNV) is a common vision-threatening complication of myopia and pathologic myopia (PM). The standard tests for diagnosing myopic CNV are fundus biomicroscopy with a slit-lamp, fluorescein angiography (FA) and optical coherence tomography (OCT). FA and OCT are generally recommended baseline diagnostic tests for myopic CNV in conjunction with color photos and clinical examination. FA demonstrates the presence, type, area and activity of myopic CNV, and helps exclude other disorders. In case of significant hemorrhage, indocyanine green angiography (ICGA) can identify the presence of lacquer cracks and/or CNV. Myopic CNV has different lesion characteristics to AMD-CNV, especially in younger individuals, but is a predominantly 'classic', 'type 2' CNV; that is, smaller than that of AMD, with minimal subretinal fluid and an absence of drusen at the typical age of onset.[8]

Guidelines
AMD
The European Society of Retina Specialists (EURETINA) guidelines for the management of neovascular age-related macular degeneration no longer recommend Macugen (pegaptanib) for the treatment of exudative AMD based on the VISION study data that indicates that it is less efficacious than other anti-VEGF agents (evidence level 1). With a short intravitreal half-life of 2-4 days, rapid systemic clearance and high systemic safety has put Lucentis (ranibizumab) as the reference standard for treatment of CNV (choroidal neovascularization).[5]

Ranibizumab has been found to penetrate the retina well after intravitreal injection and have a short intravitreal half-life (2-4 days) and rapid systemic clearance (unlike bevacizumab) making ranibizumab monotherapy a reference standard for treatment of CNV. However, the guideline indicates that ranibizumab and bevacizumab both have solid visual function benefits (evidence level 1).[5]

Aflibercept has higher binding affinity than ranibizumab and bevacizumab. Aflibercept and ranibizumab have been found to be equally effective in blocking endothelial cell proliferation and 10-fold more potent than bevacizumab (evidence level 1).[5]

Laser photocoagulation therapy and verteporfin are therapeutic options for selected patients that VEGF inhibition is not advisable (evidence level 1).[5]

Irradiation is believed to reduce the number of retreatments that are necessary, but many aspects such as delivery methods, efficacy and safety are still controversial and need further investigation.[5]

The American Academy of Ophthalmology (AAO) 2015 Intravitreal injection policy states that patients undergoing intravitreal injections require the care and judgment of an ophthalmologist experienced in diagnosing and treating retinal diseases as well as potential complications that may necessitate surgical intervention.[10]

For treatment of advanced stages of AMD (neovascular type), American Academy of Ophthalmology (AAO) preferred practice policy suggest intravitreal injection therapy using the antivascular endothelial growth factors (VEGF) agents (aflibercept, bevacizumab [off-label], or ranibizumab) as the most effective and the first line of treatment and stabilization. The VEGF inhibitors have shown improved visual and anatomic outcomes vs other therapies. Aflibercept (Eylea) has been documented as noninferior in efficacy to ranibizumab (Lucentis) in the head-to-head phase III VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) trials. The Comparison of AMD Treatment Trials (CATT) compared the safety and effectiveness of bevacizumab (Avastin- off label) and ranibizumab (Lucentis) and found that there was comparable equivalence in visual acuity improvements for monthly dosing at 1 year- similar results were reported at 2 years. These results were echoed in the 2-year inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) trial. Unlike the other anti-VEGF agents that are currently available, pegaptanib (Macugen) does not improve visual acuity in patients with new-onset neovascular AMD.[6]

The policy also addresses active choroidal neovascularization (CNV) and polypoidal choroidal vasculopathy stating: Subretinal hemorrhages are relatively common in neovascular AMD. Small subretinal hemorrhages are a sign of active CNV or polypoidal choroidal vasculopathy and may be managed with anti-VEGF therapy.[6]

AAO also indicates that the current data does not support the use of intravitreal corticosteroids in combination with anti-VEGF agents and/or with verteporfin photodynamic therapy (PDT) due to the long-term side effects of glaucoma and cataract(s) that are associated with corticosteroid use.[6]

The DENALI and MONT BLANC studies compared ranibizumab (Lucentis) in combination with verteporfin PDT (Visudyne) vs ranibizumab alone and found no significant benefit in adding PDT to anti-VEGF therapy in new-onset neovascular AMD. In the polypoidal choroidal vasculopathy variant of AMD, the EVEREST study did show that fewer injections of the anti-VEGFs were needed when combination therapy was utilized.[6]

RVO

The AAO recommends intravitreal pharmacotherapy with anti-VEGF agents as safe and effective therapy (level 1 evidence). Prolonged delay in treatment is associated with less improvement in visual acuity. Intravitreal corticosteroids also have level 1 evidence and are safe and effective, although corticosteroids are associated with increased potential ocular side effects including elevated intraocular pressure and cataracts. Laser photocoagulation remains a safe and effective therapy but results the results are not as robust as the results for anti-VEGF therapies.[11]

DME

The AAO concludes that a review of the available literature indicates that anti-VEGF pharmacotherapy delivered by intravitreal injection, is safe and efficacious treatment over 2 years for DME. Further evidence is required to support long-term safety and their comparative efficacy.[12]

Diabetic Retinopathy with DME
The AAO recommends intravitreal injections of anti-VEGF agents as an effective alternate therapy for proliferative diabetic retinopathy.[7]

Myopic Choroidal Neovascularization
Subfoveal CNV is currently treated with anti-VEGF monotherapy in newly diagnosed neovascular AMD and verteporfin PDT is utilized in unresponsive cases. Thermal laser photocoagulation surgery is no longer recommended for subfoveal CNV treatment due to poor results/benefits when used. Juxtafoveal CNV has not historically been included in studies; however, many clinicians have extrapolated the data from current trials and consider anti-VEGF agents as primary therapy for juxtafoveal lesions with verteporfin PDT as possible off-label treatment. Similar philosophies are applied with Extrafoveal CNV with anti-VEGF as first-line with laser surgery as 2nd choice. AAO recommends verteporfin/PDT for macular CNV in certain patients (e.g., classic component is $\geq$50% of the lesion and entire lesion is $\leq$5400 microns in greatest linear diameter).[6]

Bevacizumab
Bevacizumab is commonly used to treat CNV (in AMD and other diseases), DME, and RVO. Interest in bevacizumab for ocular use began due to the molecular similarity it shares with ranibizumab. Bevacizumab has a long history of safety and efficacy, albeit without FDA approval for ocular use. Based on its affordability, the world health organization has put bevacizumab and not ranibizumab in WHO model list of essential drugs. In ophthalmology, bevacizumab is typically given by transconjunctival intravitreal injections into the posterior segment. Intravitreal injections for retinal pathologies are typically administered at 4-6-week intervals, although this varies widely based on disease and response. Typical dose is 1.25 mg in 0.05 mL in adults, and half that dose in babies.[14-15]

Bevacizumab is considered efficacious for treatment of CNV and macular edema by the ophthalmologic community. As this drug has not been FDA approved for ophthalmic indications, classic clinical trials do not uniformly exist, however convincing data has been published for the most commonly treated pathologies.[14]

Age-related Macular Degeneration (neovascular with CNV): The sham injection/untreated arm of the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) trial showed vision loss of 14.9 letters from baseline over 24 months, which is often quoted as the natural history of neovascular AMD. While the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) did not have an untreated arm, it was perhaps the most well-structured clinical trial involving bevacizumab and showed a 7.8 letter gain from baseline with monthly administration. The Inhibit VEGF in the Age-Related Choroidal Neovascularization trial (IVAN) echoed this positive result.[14]

Diabetic Macular Edema (DME): The Pan-American Collaborative Retina Study Group (PACORES) trial compared monthly intravitreal bevacizumab with macular focal-grid laser photocoagulation (standard of care at that time) and showed an average of 11.86 letters gained with bevacizumab and 3.66 letters gained with focal grid laser over 24-months.[14]

Macular Edema due to Retinal Vein Occlusion: The untreated macular edema arm (Group M) of the Central Vein Occlusion Study (CVOS) trial lost approximately 5 letters from baseline. The PACORES trial for central vein occlusion, which did not have an untreated arm but had similar inclusion criteria, showed 19 letters of improvement from baseline over 12 months with monthly/as-needed intravitreal bevacizumab.[14]

Safety[1-4,13]

- **Beovu (brolucizumab-dbll)** is contraindicated in:
  - Ocular or Periocular Infections
  - Active Intraocular Inflammation
  - Hypersensitivity
- **Eylea (aflibercept)** is contraindicated in patients with:
  - Ocular or periocular infection
  - Active intraocular inflammation
  - A known hypersensitivity to aflibercept or any other excipients in Eylea
- **Lucentis (ranibizumab)** is contraindicated in patients with:
  - Ocular or periocular infections
  - A known hypersensitivity to ranibizumab or any of the excipients in Lucentis
- **Macugen (pegaptanib sodium)** is contraindicated in patients with:
  - Ocular or periocular infections
  - Known hypersensitivity to pegaptanib sodium or any other excipient in the product.
- **Susvimo** (ranibizumab) is contraindicated in patients with:
  - Periocular infections
  - Active intraocular inflammation
  - Known hypersensitivity to ranibizumab products or any of the excipients in Susvimo
- **Visudyne (verteporfin)** is contraindicated in patients with:
  - Porphyria
  - A Known hypersensitivity to any component of the preparation

References

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16. Susvimo Prescribing Information. Genentech, Inc, October 2021.

 Effective: xx/xx/xx

Document History
Original Part B Prime Standard criteria approved by P&T UM Committee 12/2020
Annual Review of Part B Prime Standard criteria, with changes to criteria, approved by UM P&T Committee 03/2021
Mid-Year Review of Part B Prime Standard criteria, with changes to criteria, approved by UM P&T Committee 06/2021
Mid-Year Review of Part B Prime Standard criteria, with changes to criteria, approved by P&T UM Committee 12/2021

Medicare Part B - Ocular Angiogenesis Inhibitors Through Bevacizumab

Coverage and policy application are contingent on National Coverage Determinations (NCD) and Local Coverage Determinations (LCD). An NCD or LCD that is applicable to the drug or product must be used in lieu of applicable medical necessity criteria. Also, please note that Prior Authorization criteria cannot be stricter than an NCD or LCD with specified step therapy requirements.

TARGET AGENT(S)

TARGET AGENT(S)	PREREQUISITE AGENT(S)
Target and prerequisite agent(s) determined by client	Target and prerequisite agent(s) determined by client
For neovascular (wet) age-related macular degeneration (AMD) • **Beovu** (brolucizumab-dbll) • **Eylea** (aflibercept) • **Lucentis** (ranibizumab) • **Macugen** (pegaptanib sodium) • **Susvimo** (ranibizumab) For macular edema following retinal vein occlusion (RVO) • **Eylea** (aflibercept) • **Lucentis** (ranibizumab) For diabetic macular edema (DME) • **Eylea** (aflibercept) • **Lucentis** (ranibizumab) For diabetic retinopathy • **Eylea** (aflibercept) • **Lucentis** (ranibizumab) For myopic choroidal neovascularization (mCNV) None	**Avastin** (bevacizumab) bevacizumab
Visudyne (verteporfin)	None

Brand (generic)	GPI	Multisource Code	HCPCS/ J Code
Beovu (brolucizumab-dbll)			
6 mg/0.05 mL) Single dose vial	86655025202020	M, N, O, or Y	J0179
Eylea (aflibercept)			
2mg/0.05 mL Single dose vial	86655010002020	M, N, O, or Y	J0178
2 mg/0.05 mL Prefilled syringe	8665501000E520	M, N, O, or Y	J0178
Lucentis (ranibizumab)			

 Effective: xx/xx/xx

0.5mg/0.05 mL Prefilled syringe	8665506000E520	M, N, O, or Y	J2778
0.3mg/0.05 mL Prefilled syringe	8665506000E510	M, N, O, or Y	J2778
0.3mg/0.05 mL Single dose vial	86655060002012	M, N, O, or Y	J2778
0.5mg/0.05 mL Single dose vial	86655060002020	M, N, O, or Y	J2778
Macugen (pegaptanib)			
0.3 mg/0.09 mL Prefilled syringe	86655050302020	M, N, O, or Y	J2503
Susvimo (ranibizumab)			
10 mg/0.1 mL implant 1st fill	86655060002040	M, N, O, or Y	TBD
10 mg/0.1 mL implant refill	86655060002042	M, N, O, or Y	TBD
Ocular implant – intravitreal reservoir	97604040002340	M, N, O, or Y	TBD
Visudyne (verteporfin)			
2 mg/mL Single dose vial	86700065002120	M, N, O, or Y	J3396

CRITERIA FOR APPROVAL

Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The requested agent is being used for ONE of the following:
    a. An FDA approved indication
    OR
    b. An indication in CMS approved compendia

    AND
2. ONE of the following:
    a. Information has been provided that indicates the patient has been treated with the requested agent in the past 365 days
    OR
    b. There is documentation that the patient has had an ineffective treatment response to the active ingredient(s) of ALL prerequisite agent(s)
    OR
    c. The patient has a documented intolerance, hypersensitivity, or FDA labeled contraindication to the active ingredient(s) of ALL prerequisite agent(s)
    OR
    d. The prescriber has submitted documentation indicating ALL prerequisite agent(s) are likely to be ineffective or are likely to cause an adverse reaction or other harm to the patient

    AND
3. The patient does NOT have any FDA labeled contraindications to the requested agent
    AND
4. The requested quantity (dose) is within FDA labeled dosing or supported in compendia for the requested indication

Length of Approval: up to 12 months

 Effective: xx/xx/xx