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Subject: Vascular Endothelial Growth Factor Inhibitors for Ocular Neovascularization

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Uncorrectable vision impairment and blindness affect more than 4.2 million individuals in the United States older than the age of 40. Age-related macular degeneration (AMD), glaucoma, cataracts, and diabetic retinopathy are the most common eye disorders in the U.S. adult population. The number of people with AMD is estimated to reach 2.95 million in 2020. AMD is the leading cause of permanent impairment of reading and fine or close-up vision among people aged 65 years and older. Vascular endothelial growth factor (VEGF) has been implicated in the pathogenesis of a variety of ocular vascular conditions characterized by choroidal neovascularization (CNV) and macular edema. VEGF is a protein that stimulates the growth, proliferation, and survival of vascular endothelial cells. Several VEGF inhibitors for ocular use have been approved for the treatment of various eye diseases. Pegaptanib sodium (Macugen) is approved by the US Food and Drug Administration (FDA) for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD) [September 2004]. Ranibizumab (Lucentis) is approved for the treatment of patients with neovascular (wet) AMD [June 2006], macular edema after retinal vein occlusion (RVO) [June 2010], diabetic macular edema (DME) [August 2012], diabetic retinopathy in patients with DME [February 2015], and myopic choroidal neovascularization (mCNV) [January 2017]. Aflibercept (Eylea) is approved for the treatment of patient with neovascular (Wet) AMD [November 2011], macular edema following central retinal vein occlusion (CRVO) [September 2012], DME [July 2014], and macular edema following RVO [October 2014, an expansion of CRVO indication]. Brolucizumab (Beovu) is approved by the FDA for the treatment of patient with Neovascular (Wet) AMD [October 2019]

In April 2017 ranibizumab (Lucentis) became the first VEGF-inhibitor to be FDA-approved for the treatment of diabetic retinopathy (DR) in patients without diabetic macular edema (DME). The approval

was based on a subgroup analysis of a secondary endpoint in the Diabetic Retinopathy Clinical Research Network's (DRCR.net) Protocol S study in which ranibizumab was found to be non-inferior to panretinal photocoagulation (PRP) in patients with proliferative diabetic retinopathy (PDR), including those with and without DME. Proliferative DR, as opposed to non-proliferative DR (NPDR), is defined by the presence of some degree of retinal neovascularization. The VEGF-inhibitors work by inhibiting angiogenesis and neovascularization. At year 2 among patients treated with ranibizumab, 31.7% (13/41) and 28.4% (42/148) of eyes in the subgroups with baseline DME and without baseline DME, respectively, had ≥ 3 -step improvement from baseline in ETDRS-DRSS (Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Score).

In May 2019 aflibercept (Eylea) became the second VEGF-inhibitor to be FDA-approved for the treatment of diabetic retinopathy (DR) in patients without diabetic macular edema (DME). The approval was based on data derived from the VIVID and VISTA studies (patients with DME and DR) and the PANORAMA study. A major difference between the aflibercept and ranibizumab approvals is that aflibercept was evaluated in a randomized, multi-center, double-masked, controlled study specifically looking at patients with moderately-severe to severe nonproliferative diabetic retinopathy (NPDR) (ETDRS-DRSS of 47 or 53), without central-involved DME [i.e., PANORAMA trial]. A total of 402 randomized patients were evaluable for efficacy. Patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: (1) 3 initial monthly aflibercept 2 mg injections followed by one injection after 8 weeks and then one injection every 16 weeks (EYLEA 2Q16); (2) 5 monthly aflibercept 2 mg injections followed by one injection every 8 weeks (EYLEA 2Q8); and (3) sham treatment. The primary efficacy endpoint was the proportion of patients who improved by ≥ 2 steps on the DRSS from baseline to week 24 in the combined aflibercept groups and at week 52 in the 2Q16 and 2Q8 groups individually vs. sham. A key secondary endpoint was the proportion of patients developing the composite endpoint of proliferative diabetic retinopathy or anterior segment neovascularization through week 52. Results are seen in Table 1 below.

	Week 24		Week 52		
	Eylea Combined (n=269)	Control (n=133)	Eylea 2Q16 (n=135)	Eylea 2Q8 (n=134)	Control (n=133)
Patients with a ≥ 2 -step improvement on ETDRS-DRSS from Baseline	58%	6%	65%	80%	15%
Composite Endpoint of Developing PDR or ASNV	N/A	N/A	4%	2.4%	20.1%
Development of PDR	N/A	N/A	1.6%	0%	11.9%

PDR = Proliferative Diabetic Retinopathy; ASNV = Anterior Segment Neovascularization

A brief overview of covered products is provided in Table 2.

Table 2

Review of covered products	
Product	Notes
Aflibercept (Eylea)	<ul style="list-style-type: none"> Humanized recombinant fusion protein Inhibits VEGF-A and placental growth factor
Bevacizumab (Avastin) and bevacizumab biosimilars	<ul style="list-style-type: none"> Recombinant humanized monoclonal antibody Works by binding to and inhibiting the biologic activity of VEGF to prevent interaction with receptors on the surface of endothelial cells

[bevacizumab-awwb (Mvasi) and bevacizumab-awwb (Zirabev)]	<ul style="list-style-type: none"> Prevents cell proliferation and new blood vessel formation Produced in a Chinese hamster ovary mammalian cell expression system
Brolucizumab (Beovu)	<ul style="list-style-type: none"> Recombinant humanized monoclonal single-chain Fv antibody fragment Binds to the three major isoforms of VEGF-A (e.g., VEGF110, VEGF121, and VEGF165) Suppresses endothelial cell proliferation, neovascularization, and vascular permeability
Pegaptanib (Macugen)	<ul style="list-style-type: none"> Pegylated modified oligonucleotide Selectively binds to extracellular VEGF-165, the major pathological VEGF isoform for wet AMD
Ranibizumab (Lucentis)	<ul style="list-style-type: none"> Recombinant humanized monoclonal antibody – a fragment derived from the same parent molecule as bevacizumab Binds to all active isoforms of VEGF Reduces endothelial cell proliferation, vascular leakage, and new blood vessel formation

POSITION STATEMENT:

The initiation of aflibercept, bevacizumab (including biosimilars), brolucizumab, pegaptanib, or ranibizumab **meets the definition of medical necessity** for members meeting agent-specific criteria outlined in Table 3, **AND** none of these products are used concurrently in combination with each other in the same eye, or used in combination with dexamethasone (Ozurdex) implant or fluocinolone acetonide (Iluvien, Retisert, Yutiq) implant in the same eye [with the exception of bevacizumab or bevacizumab biosimilars which may be used as rescue therapy for rare members who are refractory to the implant].

Table 3

Criteria for use	
Product	Criteria
Aflibercept (Eylea)	<p>Use is a medical necessity for the following indications in members without ocular or periocular infections and dosage does not exceed 2 mg to each eye every 28 days:</p> <ol style="list-style-type: none"> Neovascular (wet) age-related macular degeneration (ARMD/AMD) Macular edema following central retinal vein occlusion (CRVO) Macular edema following branch retinal vein occlusion (BRVO) Diabetic macular edema (DME) Diabetic retinopathy (DR) in members with DME Moderately-severe to severe nonproliferative diabetic retinopathy (NPDR) (with or without macular edema) – the member's Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale score must be provided Proliferative diabetic retinopathy (PDR) as defined by the presence of retinal neovascularization (with or without macular edema)

<p>Bevacizumab (Avastin) and bevacizumab biosimilars [bevacizumab-awwb (Mvasi) and bevacizumab-awwb (Zirabev)]</p>	<p>Use is a medical necessity for the below listed non-FDA labeled* indications in members without ocular or periocular infections:</p> <ol style="list-style-type: none"> 1. Neovascular (wet) age-related macular degeneration (ARMD/AMD) 2. Macular edema following branch retinal vein occlusion (BRVO) 3. Macular edema following central retinal vein occlusion (CRVO) 4. Diabetic macular edema (DME) 5. Diabetic retinopathy (DR) 6. Proliferative diabetic retinopathy (PDR) as defined by the presence of retinal neovascularization (with or without macular edema) 7. Proliferative diabetic retinopathy requiring treatment with retinal laser photocoagulation or vitrectomy as a single preoperative dose 8. Secondary angle-closure glaucoma resulting from neovascularization (i.e., neovascular glaucoma) 9. Radiation retinopathy 10. Retinopathy of prematurity when first-line treatment with laser photocoagulation is not possible (e.g., opaque cornea or lens, poor pupillary dilation) and treatment is given as a single dose 11. Choroidal neovascularization secondary to ANY of the following: <ol style="list-style-type: none"> a. Pathologic myopia (i.e., myopic choroidal neovascularization) b. Ocular histoplasmosis syndrome (OHS) c. Angioid streaks/pseudoxanthoma elasticum <p>*Physicians should provide appropriate informed consent with respect to the off-label use of bevacizumab.</p>
<p>Brolucizumab (Beovu)</p>	<p>Use is a medical necessity for the following indications in members without ocular or periocular infections and dosage does not exceed 6 mg to each eye every 4 weeks (28 days) for the first three doses, and then every 8 weeks (56 days) for subsequent doses:</p> <ol style="list-style-type: none"> 1. Neovascular (wet) age-related macular degeneration (ARMD/AMD)
<p>Pegaptanib (Macugen)</p>	<p>Use is a medical necessity for the following indications in members without ocular or periocular infections and dosage does not exceed 0.3 mg to each eye every 6 weeks (45 days):</p> <ol style="list-style-type: none"> 1. Neovascular (wet) age-related macular degeneration (ARMD/AMD) 2. Diabetic macular edema (DME)
<p>Ranibizumab (Lucentis)</p>	<p>Use is a medical necessity for the following indications in members without ocular or periocular infections:</p> <ol style="list-style-type: none"> 1. Neovascular (wet) age-related macular degeneration (ARMD/AMD) and dosage does not exceed 0.5 mg to each eye every 28 days 3. Macular edema following branch retinal vein occlusion (BRVO) and

	<p>dosage does not exceed 0.5 mg to each eye every 28 days</p> <ol style="list-style-type: none"> 4. Macular edema following central retinal vein occlusion (CRVO) and dosage does not exceed 0.5 mg every to each eye 28 days 5. Diabetic macular edema (DME) and dosage does not exceed 0.3 mg to each eye every 28 days 6. Diabetic retinopathy (DR) in members with DME and dosage does not exceed 0.3 mg to each eye every 28 days 7. Proliferative diabetic retinopathy (PDR) as defined by the presence of retinal neovascularization (with or without macular edema) and dosage does not exceed 0.3 mg to each eye every 28 days 8. Choroidal neovascularization secondary to ANY of the following and dosage does not exceed 0.5 mg to each eye every 28 days: <ol style="list-style-type: none"> a. Pathologic myopia (i.e., myopic choroidal neovascularization) b. Ocular histoplasmosis syndrome (OHS) c. Angioid streaks/pseudoxanthoma elasticum
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Approval duration: 1 year (except retinopathy of prematurity and pre-operative use for diabetic retinopathy requiring treatment with retinal laser photocoagulation or vitrectomy; for these indications only a single dose will be approved)

Continuation of aflibercept, bevacizumab (including biosimilars), brolucizumab, pegaptanib, or ranibizumab **meets the definition of medical necessity** for members meeting all of the following criteria:

1. An authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for an indication listed in Table 3 [except for the use of bevacizumab (including biosimilars) for retinopathy of prematurity or as a single preoperative dose – see initiation criteria], **OR** the member has previously met all indication-specific initiation criteria
2. Member has had improvement or stabilization of visual function as compared to before treatment
3. The dosage does not exceed the drug- and indication-specific limit listed in Table 3
4. None of the agents are used in combination with each other in the same eye
5. Beovu, Eylea, Lucentis, or Macugen are not used in combination with dexamethasone (Ozurdex) implant or fluocinolone acetonide (Iluvien Retisert, Yutiq) implant in the same eye*

**Bevacizumab (including biosimilars) may be used as rescue therapy for rare members who are refractory to the implant.*

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Dosage and administration varies considerably with each product. A brief overview of selected products is provided in Table 3, but it is **strongly recommended** the prescriber reference the product-specific labeling for complete dosing and administration instructions.

Table 4

Dosage and administration	
Product	Dosing/Administration
Aflibercept (Eylea)	<p>Neovascular (Wet) Age-Related Macular Degeneration (AMD)</p> <ul style="list-style-type: none"> • 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months) • May be dosed as frequently as 2 mg every 4 weeks (monthly); however, additional efficacy was not demonstrated in most patients when 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). Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly. <p>Macular Edema Following Retinal Vein Occlusion (RVO) – includes both central and branch RVO (CRVO and BRVO)</p> <ul style="list-style-type: none"> • 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly) <p>Diabetic Macular Edema (DME) or Diabetic Retinopathy (DR)</p> <ul style="list-style-type: none"> • 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first five injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months) • May be dosed as frequently as 2 mg every 4 weeks (monthly); however, additional efficacy was not demonstrated in most patients when 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).
Bevacizumab (Avastin) and bevacizumab biosimilars [bevacizumab-awwb (Mvasi) and bevacizumab-awwb (Zirabev)]	<p>Off-label dosing recommendations</p> <ul style="list-style-type: none"> • 1.25 mg (0.05 mL) administered by intravitreal injection
Brolucizumab (Beovu)	<p>Neovascular (Wet) Age-Related Macular Degeneration (AMD)</p> <ul style="list-style-type: none"> • 6 mg (0.05 mL) administered by intravitreal injection monthly (approximately every 25 to 31 days) for the first three doses, followed by

	one dose of 6 mg (0.05 mL) every 8 to 12 weeks.
Pegaptanib (Macugen)	<p>Neovascular (Wet) Age-Related Macular Degeneration (AMD)</p> <ul style="list-style-type: none"> 0.3 mg should be administered once every six weeks by intravitreal injection into the eye to be treated
Ranibizumab (Lucentis)	<p>Neovascular (Wet) Age-Related Macular Degeneration (AMD)</p> <ul style="list-style-type: none"> 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days) Although not as effective, patients may be treated with three monthly doses followed by less frequent dosing with regular assessment. In the nine months after three initial monthly doses, less frequent dosing with 4-5 doses on average is expected to maintain visual acuity while monthly dosing may be expected to result in an additional average 1-2 letter gain. Patients should be assessed regularly Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Compared to continued monthly dosing, dosing every 3 months over the next 9 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average. Patients should be assessed regularly <p>Macular Edema Following Retinal Vein Occlusion (RVO) – includes both central and branch RVO (CRVO and BRVO)</p> <ul style="list-style-type: none"> 0.5 mg (0.05 mL of 10 mg/mL solution) administered by intravitreal injection once a month (approximately 28 days) <p>Diabetic Macular Edema (DME) or Diabetic Retinopathy (DR)</p> <ul style="list-style-type: none"> 0.3 mg (0.05 mL of 6 mg/mL solution) administered by intravitreal injection once a month (approximately 28 days) <p>Myopic Choroidal Neovascularization (mCNV)</p> <ul style="list-style-type: none"> 0.5 mg (0.05 mL of 10 mg/mL solution) administered by intravitreal injection once a month (approximately 28 days) for up to 3 months. May retreat if needed.

PRECAUTIONS:

Specific precautions and warnings are highlighted in Table 5.

Table 5

Precautions and warnings	
Product	Precautions/Warnings
Aflibercept (Eylea)	Contraindications

	<ul style="list-style-type: none"> • Ocular or periocular infection • Active intraocular inflammation • Hypersensitivity to aflibercept or any of the excipients. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation. <p>Precautions/Warnings</p> <ul style="list-style-type: none"> • Endophthalmitis and Retinal Detachments - Intravitreal injections, including those with aflibercept, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. • Increases in Intraocular Pressure - Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately. • Thromboembolic Events - There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.
<p>Brolucizumab (Beovu)</p>	<p>Contraindications</p> <ul style="list-style-type: none"> • Ocular or periocular infections • Active intraocular inflammation • Hypersensitivity to brolucizumab or any other excipient in this product <p>Precautions/Warnings</p> <ul style="list-style-type: none"> • Endophthalmitis and Retinal Detachments - Intravitreal injections, including those with brolucizumab, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. • Increase in Intraocular Pressure - Acute increases in intraocular pressure (IOP) have been seen within 30 minutes of an intravitreal injection. Sustained IOP increases have also been reported. Both IOP and perfusion of the optic nerve head must be monitored and managed appropriately. • Thromboembolic Events - Although there was a low rate of arterial thromboembolic events (ATEs) observed in the brolucizumab clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The ATE rate in the two controlled 96-week neovascular AMD studies (HAWK and HARRIER) during the first 96-weeks was 4.5% (33 of 730) in the pooled brolucizumab arms compared with 4.7% (34 of 729) in the pooled aflibercept arms.

<p>Pegaptanib (Macugen)</p>	<p>Contraindications</p> <ul style="list-style-type: none"> • Ocular or periocular infection • Hypersensitivity to pegaptanib sodium or any other excipient in this product <p>Precautions/Warnings</p> <ul style="list-style-type: none"> • Endophthalmitis - Intravitreal injections, including those with pegaptanib, have been associated with endophthalmitis. Proper aseptic injection technique should always be utilized when administering. In addition, patients should be monitored during the week following the injection to permit early treatment, should an infection occur. • Increases in Intraocular Pressure - Increases in intraocular pressure have been seen within 30 minutes of an intravitreal injection. Therefore, intraocular pressure as well as the perfusion of the optic nerve head should be monitored and managed appropriately. • Anaphylaxis - Rare cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been reported in the postmarketing experience following the pegaptanib intravitreal administration procedure.
<p>Ranibizumab (Lucentis)</p>	<p>Contraindications</p> <ul style="list-style-type: none"> • Ocular or periocular infection • Hypersensitivity to ranibizumab or any of the excipients. Hypersensitivity reactions may manifest as severe intraocular inflammation. <p>Precautions/Warnings</p> <ul style="list-style-type: none"> • Endophthalmitis and Retinal Detachments - Intravitreal injections, including those with ranibizumab, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering. In addition, patients should be monitored following the injection to permit early treatment should an infection occur. • Increases in Intraocular Pressure - Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated. Monitor intraocular pressure prior to and following intravitreal injection and manage appropriately. • Thromboembolic Events - Although there was a low rate of arterial thromboembolic events (ATEs) observed in the clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). • Fatal Events in Patients with Diabetic Macular Edema and Diabetic Retinopathy at Baseline - Fatal events occurred more frequently in patients with DME and DR at baseline, who were treated monthly with ranibizumab as compared with control. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and

	intravitreal use of VEGF inhibitors cannot be excluded.
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BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J0178	Injection, aflibercept, 1 mg
J0179	Injection, brolocizumab-dblI, 1 mg
J2503	Injection, pegaptanib sodium, 0.3 mg
J2778	Injection, ranibizumab, 0.1 mg

NOTE: The use of bevacizumab and bevacizumab biosimilars for non-FDA labeled ophthalmic indications should be reported using the unclassified HCPCS code J3490 or, for Outpatient Hospital ONLY, either J3490 or C9257. Do **NOT** use HCPCS code J9035 [injection, bevacizumab, 10 mg], Q5107 [injection, bevacizumab-awwb, biosimilar, (mvasi), 10 mg], or Q5118 [injection, bevacizumab-bvzr, biosimilar, (Zirabev), 10 mg] since the agent has been processed by a pharmacist.

ICD-10 Diagnosis Codes That Support Medical Necessity for Bevacizumab (Avastin) and Bevacizumab Biosimilars [bevacizumab-awwb (Mvasi) and bevacizumab-awwb (Zirabev)] (all J3490):

B39.4	Histoplasmosis capsulati, unspecified
B39.5	Histoplasmosis duboisii
B39.9	Histoplasmosis, unspecified
E08.311	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy with macular edema
E08.3211 – E08.3219	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy with macular edema
E08.3311 – E08.3319	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy with macular edema
E08.3411 – E08.3419	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy with macular edema
E08.3511 – E08.3599	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy
E09.311	Drug or chemical induced diabetes mellitus with unspecified diabetic retinopathy with macular edema
E09.3211 – E09.3219	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E09.3311 – E09.3319	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E09.3411 – E09.3419	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E09.3511 – E09.3599	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy
E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E10.3211 – E09.3219	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with

	macular edema
E10.3311 – E10.3319	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E10.3411 – E10.3419	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E10.3511 – E10.3599	Type 1 diabetes mellitus with proliferative diabetic retinopathy
E11.311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E11.3211 – E11.3219	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E11.3311 – E11.3319	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E11.3411 – E11.3419	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E11.3511 – E11.3599	Type 2 diabetes mellitus with proliferative diabetic retinopathy
E13.311	Other specified diabetes mellitus with unspecified diabetic retinopathy with macular edema
E13.3211 – E13.3219	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E13.3311 – E13.3319	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E13.3411 – E13.3419	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E13.3511 – E13.3599	Other specified diabetes mellitus with proliferative diabetic retinopathy
H32	Chorioretinal disorders in diseases classified elsewhere
H34.8110	Central retinal vein occlusion, right eye, with macular edema
H34.8111	Central retinal vein occlusion, right eye, with retinal neovascularization
H34.8120	Central retinal vein occlusion, left eye, with macular edema
H34.8121	Central retinal vein occlusion, left eye, with retinal neovascularization
H34.8130	Central retinal vein occlusion, bilateral, with macular edema
H34.8131	Central retinal vein occlusion, bilateral, with retinal neovascularization
H34.8190	Central retinal vein occlusion, unspecified eye, with macular edema
H34.8191	Central retinal vein occlusion, unspecified eye, with retinal neovascularization
H34.821	Venous engorgement, right eye
H34.822	Venous engorgement, left eye
H34.823	Venous engorgement, bilateral
H34.829	Venous engorgement, unspecified eye
H34.8310	Tributary (branch) retinal vein occlusion, right eye, with macular edema
H34.8311	Tributary (branch) retinal vein occlusion, right eye, with retinal neovascularization
H34.8320	Tributary (branch) retinal vein occlusion, left eye, with macular edema
H34.8321	Tributary (branch) retinal vein occlusion, left eye, with retinal neovascularization
H34.8330	Tributary (branch) retinal vein occlusion, bilateral, with macular edema
H34.8331	Tributary (branch) retinal vein occlusion, bilateral, with retinal neovascularization
H34.8390	Tributary (branch) retinal vein occlusion, unspecified eye, with macular edema

H34.8391	Tributary (branch) retinal vein occlusion, unspecified eye, with retinal neovascularization
H35.00 - H35.019	Background retinopathy and retinal vascular changes [for radiation retinopathy ONLY]
H35.051	Retinal neovascularization, unspecified, right eye
H35.052	Retinal neovascularization, unspecified, left eye
H35.053	Retinal neovascularization, unspecified, bilateral
H35.059	Retinal neovascularization, unspecified, unspecified eye
H35.101 – H35.179	Retinopathy of prematurity
H35.3210 – H35.3293	Exudative age-related macular degeneration
H35.33	Angioid streaks of macula
H35.351 - H35.359	Cystoid macular degeneration
H35.81	Retinal edema
H40.51X1 - H40.51X4	Glaucoma secondary to other eye disorders, right eye
H40.52X1 - H40.52X4	Glaucoma secondary to other eye disorders, left eye
H40.53X1 - H40.53X4	Glaucoma secondary to other eye disorders, bilateral
H40.60X1 - H40.60X4	Glaucoma secondary to drugs, unspecified eye
H40.89	Other specified glaucoma
H44.2A1	Degenerative myopia with choroidal neovascularization, right eye
H44.2A2	Degenerative myopia with choroidal neovascularization, left eye
H44.2A3	Degenerative myopia with choroidal neovascularization, bilateral
H44.2A9	Degenerative myopia with choroidal neovascularization, unspecified eye
T66.XXXA - T66.XXXS	Radiation sickness, unspecified [for radiation retinopathy ONLY]

ICD-10 Diagnosis Codes That Support Medical Necessity for Brolucizumab (Beovu) (J3590):

H35.3210 – H35.3293	Exudative age-related macular degeneration
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ICD-10 Diagnosis Codes That Support Medical Necessity for Ranibizumab (Lucentis)(J2778):

B39.4	Histoplasmosis capsulati, unspecified
B39.5	Histoplasmosis duboisii
B39.9	Histoplasmosis, unspecified
E08.311	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy with macular edema
E08.3211 – E08.3219	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy with macular edema
E08.3311 – E08.3319	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy with macular edema
E08.3411 – E08.3419	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy with macular edema
E08.3511 – E08.3599	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy
E09.311	Drug or chemical induced diabetes mellitus with unspecified diabetic retinopathy with macular edema
E09.3211 – E09.3219	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic

	retinopathy with macular edema
E09.3311 – E09.3319	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E09.3411 – E09.3419	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E09.3511 – E09.3599	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy
E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E10.3211 – E09.3219	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E10.3311 – E10.3319	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E10.3411 – E10.3419	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E10.3511 – E10.3599	Type 1 diabetes mellitus with proliferative diabetic retinopathy
E11.311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E11.3211 – E11.3219	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E11.3311 – E11.3319	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E11.3411 – E11.3419	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E11.3511 – E11.3599	Type 2 diabetes mellitus with proliferative diabetic retinopathy
E13.311	Other specified diabetes mellitus with unspecified diabetic retinopathy with macular edema
E13.3211 – E13.3219	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E13.3311 – E13.3319	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E13.3411 – E13.3419	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E13.3511 – E13.3599	Other specified diabetes mellitus with proliferative diabetic retinopathy
H34.8110	Central retinal vein occlusion, right eye, with macular edema
H34.8120	Central retinal vein occlusion, left eye, with macular edema
H34.8130	Central retinal vein occlusion, bilateral, with macular edema
H34.8190	Central retinal vein occlusion, unspecified eye, with macular edema
H34.8310	Tributary (branch) retinal vein occlusion, right eye, with macular edema
H34.8320	Tributary (branch) retinal vein occlusion, left eye, with macular edema
H34.8330	Tributary (branch) retinal vein occlusion, bilateral, with macular edema
H34.8390	Tributary (branch) retinal vein occlusion, unspecified eye, with macular edema
H35.3210 – H35.3293	Exudative age-related macular degeneration
H35.33	Angioid streaks of macula
H44.2A1	Degenerative myopia with choroidal neovascularization, right eye
H44.2A2	Degenerative myopia with choroidal neovascularization, left eye
H44.2A3	Degenerative myopia with choroidal neovascularization, bilateral

H44.2A9	Degenerative myopia with choroidal neovascularization, unspecified eye
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ICD-10 Diagnosis Codes That Support Medical Necessity for Aflibercept (Eylea)(J0178):

E08.311	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy with macular edema
E08.3211 – E08.3219	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy with macular edema
E08.3311 – E08.3319	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy with macular edema
E08.3411 – E08.3419	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy with macular edema
E08.3511 – E08.3419	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema
E09.311	Drug or chemical induced diabetes mellitus with unspecified diabetic retinopathy with macular edema
E09.3211 – E09.3219	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E09.3311 – E09.3319	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E09.3411 – E09.3419	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E09.3511 – E09.3519	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema
E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E10.3211 – E10.3219	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E10.3311 – E10.3319	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E10.3411 – E10.3419	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E10.3511 – E10.3519	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema
E11.311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E11.3211 – E11.3219	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E11.3311 – E11.3319	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E11.3411 – E11.3419	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E11.3511 – E11.3519	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema
E13.311	Other specified diabetes mellitus with unspecified diabetic retinopathy with macular edema
E13.3211 – E13.3219	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy

	with macular edema
E13.3311 – E13.3319	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E13.3411 – E13.3419	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E13.3511 – E13.3519	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema
H34.8110	Central retinal vein occlusion, right eye, with macular edema
H34.8120	Central retinal vein occlusion, left eye, with macular edema
H34.8130	Central retinal vein occlusion, bilateral, with macular edema
H34.8190	Central retinal vein occlusion, unspecified eye, with macular edema
H34.8310	Tributary (branch) retinal vein occlusion, right eye, with macular edema
H34.8320	Tributary (branch) retinal vein occlusion, left eye, with macular edema
H34.8330	Tributary (branch) retinal vein occlusion, bilateral, with macular edema
H34.8390	Tributary (branch) retinal vein occlusion, unspecified eye, with macular edema
H35.3210 – H35.3293	Exudative age-related macular degeneration

ICD-10 Diagnosis Codes That Support Medical Necessity for Pegaptanib (Macugen)(J2503):

E08.311	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy with macular edema
E08.3211 – E08.3219	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy with macular edema
E08.3311 – E08.3319	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy with macular edema
E08.3411 – E08.3419	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy with macular edema
E08.3511 – E08.3519	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema
E09.311	Drug or chemical induced diabetes mellitus with unspecified diabetic retinopathy with macular edema
E09.3211 – E09.3219	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E09.3311 – E09.3319	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E09.3411 – E09.3419	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E09.3511 – E09.3519	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema
E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E10.3211 – E10.3219	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E10.3311 – E10.3319	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E10.3411 – E10.3419	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema

E10.3511 – E10.3519	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema
E11.311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E11.3211 – E11.3219	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E11.3311 – E11.3319	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E11.3411 – E11.3419	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E11.3511 – E11.3519	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema
E13.311	Other specified diabetes mellitus with unspecified diabetic retinopathy with macular edema
E13.3211 – E13.3219	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E13.3311 – E13.3319	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E13.3411 – E13.3419	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E13.3511 – E13.3519	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema
H35.3210 – H35.3293	Exudative age-related macular degeneration

REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: Medical necessity is determined using any applicable NCD or LCD and then Step Therapy Requirements for Medicare Outpatient (Part B) Medications outlined in Policy (09-J3000-39).

DEFINITIONS:

Macular edema - swelling of the retina due to leaking of fluid from blood vessels within the macula (the central portion of the retina). Diabetic macular edema (DME) is macular edema that occurs in patients with diabetes.

Retinal vein occlusion - a blockage of one or more veins that carry blood away from the retina. Central retinal vein occlusion (CRVO) occurs when the blockage is in the main vein in the retina. Branch retinal vein occlusion (BRVO) occurs when the blockage is one of the smaller veins attached to the main vein in the retina

RELATED GUIDELINES:

None

OTHER:

Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale

DRSS Level/severity	Definition
10 No retinopathy	<ul style="list-style-type: none">• Diabetic retinopathy absent
20 Very mild NPDR	<ul style="list-style-type: none">• Microaneurysms only
35 Mild NPDR	<ul style="list-style-type: none">• Hard exudates, cotton-wool spots, and/or mild retinal hemorrhages
47 Moderate NPDR	<ul style="list-style-type: none">• Retinal hemorrhages: moderate in 4 quadrants or severe in 1 quadrant• Mild intraretinal microvascular abnormalities in 4 quadrants
53 Severe NPDR	<ul style="list-style-type: none">• ≥ 2 level 47 characteristics• Severe retinal hemorrhages in 4 quadrants• Moderate to severe intraretinal microvascular abnormalities in ≥ 1 quadrant• Venous beading (or loops) in at least 2 quadrants
61 Mild PDR	<ul style="list-style-type: none">• New vessels < 0.5 disc area in ≥ 1 quadrant
65 Moderate PDR	<ul style="list-style-type: none">• New vessels ≥ 1 disc diameters of the optic disc in ≥ 1 quadrant < 0.25-0.33 disc area• New vessels elsewhere in ≥ 0.5 disc area in ≥ 1 quadrant
71, 75 High-risk PDR	<ul style="list-style-type: none">• New vessel ≥ 1 disc diameter of the optic disc ≥ 0.5 disc area plus preretinal hemorrhage or vitreous hemorrhage, or preretinal hemorrhage or vitreous hemorrhage obscuring ≥ 1 disc area
81, 85 Advanced PDR	<ul style="list-style-type: none">• Fundus partially obscured by vitreous hemorrhage and either new vessels ungradable or retina detached at the center of the macula

DRSS = diabetic retinopathy severity score; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/13/19.

GUIDELINE UPDATE INFORMATION:

12/15/12	New Medical Coverage Guideline.
01/01/13	Annual HCPCS Update: added HCPCS code J0178 and removed code Q2046.
01/15/14	Review and revision to guideline; consisting of reformatting and revising the position statement, dosage, administration, precautions sections and updating the references.
10/15/14	Revision to guideline; consisting of position statement, dosing/administration.
01/15/15	Review and revision to guideline; consisting of updating references.
02/15/15	Revision to guideline; consisting of updating position statement and dosing/administration.
03/15/15	Revision to guideline; consisting of position statement.
06/15/15	Revision to guideline; consisting of position statement and updating references.
08/15/15	Revision to guideline; consisting of updating coding.
10/01/15	Revision consisting of update to Program Exceptions section.
11/01/15	Revision: ICD-9 Codes deleted.
01/15/16	Review and revision to guideline consisting of updates to position statement, coding/billing, and references.
08/15/16	Revision to guideline consisting of updating coding information.

10/01/16	Revision: ICD-10 code updates.
01/15/17	Review and revision to guideline consisting of position statement, coding/billing, and references.
06/15/17	Revision to guideline consisting of updates to the position statement, description section, dosage/administration, billing/coding, and references based on a new FDA-approved indication for ranibizumab (Lucentis).
05/15/18	Review and revision to guideline consisting of position statement, coding/billing, and references.
09/15/18	Revision to guideline consisting of updates to the coding/billing section.
05/15/19	Review and revision to guideline consisting of updating the dosage/administration and references.
07/15/19	Revision to guideline consisting of updates to the position statement, description section, dosage/administration, billing/coding, and references based on a new FDA-approved indication for aflibercept (Eylea). Update to Program Exceptions.
10/15/19	Revision to guideline consisting of updates to the position statement and coding/billing section.
12/15/19	Revision to guideline consisting of updates to the description, position statement, dosage/administration, billing/coding, and references based on new FDA-approval of brolocizumab (Beovu) and the inclusion of bevacizumab biosimilars.
01/01/20	Revision: HCPCS code updates. Added J0179 and deleted J3590.