09-J1000-78

Original Effective Date: 12/15/12

Reviewed: 11/10/21

Revised: 04/01/22

Subject: Vascular Endothelial Growth Factor Inhibitors for Ocular Neovascularization

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

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]. Aflibercept (Eylea) was granted orphan designation by the FDA for the treatment of retinopathy of prematurity in July 2019. Brolucizumab (Beovu) is approved by the FDA for the treatment of patient with Neovascular (Wet) AMD [October 2019]. In October 2021, the FDA approved a more concentrated formulation of ranibizumab (brand name Susvimo) for use in an ocular

implant (the Susvimo implant) for the treatment of patients with neovascular (wet) AMD who have previously responded to at least two intravitreal injections of a VEGF inhibitor. Susvimo has a concentration of 100 mg/mL while Lucentis has a concentration of either 6 mg/mL or 10 mg/mL The initial fill and ocular implant insertion, and implant removal procedures (if medically necessary), must be performed in an operating room using aseptic technique by a physician experienced in vitreoretinal surgery. The refill-exchange procedures are done every 24 weeks (6 months) and must be done by a physician experienced in ophthalmic surgery. In a minority of patients (about 5%), supplemental treatment with Lucentis 0.5 mg injections may be necessary while the Susvimo implant is in place. Susvimo has a boxed warning for endophthalmitis because the implant has been associated with a 3-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab.

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.

Table 1

	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)	• Humanized recombinant fusion protein • Inhibits VEGF-A and placental growth factor
Bevacizumab (Avastin) and bevacizumab biosimilars [bevacizumab-awwb (Mvasi) and bevacizumab-awwb (Zirabev)]	• 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 • Prevents cell proliferation and new blood vessel formation • Produced in a Chinese hamster ovary mammalian cell expression system
Brolucizumab (Beovu)	• 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)	• Pegylated modified oligonucleotide • Selectively binds to extracellular VEGF-165, the major pathological VEGF isoform for wet AMD
Ranibizumab (Lucentis)	• 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 [with the exception of Susvimo and Lucentis, for which Lucentis may be used as periodic rescue therapy for breakthrough symptoms in patients receiving treatment with Susvimo], or used in combination with dexamethasone (Ozurdex) implant or fluocinolone acetonide (Iluvien, Retisert, Yutiq) implant in the same eye as continuous maintenance therapy [with the exception of bevacizumab or bevacizumab biosimilars which may be used as rescue therapy for rare members who are refractory to the implant]. For Iluvien only, aflibercept, bevacizumab (including biosimilars), brolucizumab, pegaptanib, or ranibizumab may be used as periodic rescue therapy for breakthrough symptoms.

Table 3

Criteria for use	
Product	**Criteria**
Aflibercept (Eylea)	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 (except retinopathy of prematurity which is a single dose only per eye): 1. Neovascular (wet) age-related macular degeneration (ARMD/AMD) 2. Macular edema following central retinal vein occlusion (CRVO) 3. Macular edema following branch retinal vein occlusion (BRVO) 4. Diabetic macular edema (DME) 5. Diabetic retinopathy (DR) in members with DME 6. Moderately-severe to severe non-proliferative diabetic retinopathy (NPDR) (with or without macular edema) – the member's Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale score demonstrating at least moderately-severe disease (i.e., 47 or greater) must be provided 7. Proliferative diabetic retinopathy (PDR) as defined by the presence of retinal neovascularization (with or without macular edema) 8. 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
Bevacizumab (Avastin) and bevacizumab biosimilars [bevacizumab-awwb (Mvasi) and	Use is a medical necessity for the below listed non-FDA labeled* indications in members without ocular or periocular infections: 1. Neovascular (wet) age-related macular degeneration (ARMD/AMD) 2. Macular edema following branch retinal vein occlusion (BRVO)

bevacizumab-awwb (Zirabev)]	3. Macular edema following central retinal vein occlusion (CRVO) 4. Diabetic macular edema (DME) 5. Diabetic retinopathy (DR) 6. Neovascularization of the iris (NVI) (rubeosis iridis) 7. Polypoidal choroidal vasculopathy (PCV) 8. Proliferative diabetic retinopathy (PDR) as defined by the presence of retinal neovascularization (with or without macular edema) 9. Proliferative diabetic retinopathy requiring treatment with retinal laser photocoagulation or vitrectomy as a single preoperative dose 10. Secondary angle-closure glaucoma resulting from neovascularization (i.e., neovascular glaucoma) 11. Radiation retinopathy 12. 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 13. Choroidal neovascularization secondary to **ANY** of the following: a. Pathologic myopia (i.e., myopic choroidal neovascularization) b. Ocular histoplasmosis syndrome (OHS) c. Angioid streaks/pseudoxanthoma elasticum **Physicians should provide appropriate informed consent with respect to the off-label use of bevacizumab.*
Brolucizumab (Beovu)	Use is a medical necessity for the following indication(s) 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: 1. Neovascular (wet) age-related macular degeneration (ARMD/AMD)
Pegaptanib (Macugen)	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): 1. Neovascular (wet) age-related macular degeneration (ARMD/AMD) 2. Diabetic macular edema (DME)
Ranibizumab (Lucentis) [6 mg/ml and 10 mg/mL solution]	Use is a medical necessity for the following indications in members without ocular or periocular infections: 1. Neovascular (wet) age-related macular degeneration (ARMD/AMD) and dosage does not exceed 0.5 mg to each eye every 28 days

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.