**INTRAVITREAL ANGIOGENESIS INHIBITORS FOR TREATMENT OF RETINAL AND CHOROIDAL VASCULAR CONDITIONS**

**Description:** Formation of new blood vessels through neovascularization or angiogenesis in the posterior segment of the eye, particularly in the region of the retina, can result in a number of conditions that may severely impair vision. Conditions related to neovascularization of the eye include the “wet” form of age-related macular degeneration (AMD) and macular edema. The proliferation of blood vessels behind the retina is due, in part, to the activity of vascular endothelial growth factor (VEGF) family members, which induce angiogenesis and increase vascular permeability and inflammation of the choroid, retina, and macula.

Several VEGF inhibitors can be administered by intravitreal injection for treatment of ophthalmic disorders characterized by retinal and choroidal neovascularization. Pegaptanib sodium (Macugen®) is a pegylated modified oligonucleotide, or aptamer, that binds and inhibits extracellular VEGF. Pegaptanib sodium was FDA-approved in 2004 for treatment of neovascular (wet) AMD.

Aflibercept (Eylea™) is a recombinant fusion protein, consisting of components of human VEGF receptors and human IgG, which binds and inhibits VEGF family members. It received FDA-approval in 2012 for the treatment of patients with neovascular (wet) AMD and for treatment of macular edema following central retinal vein occlusion (CRVO). Another aflibercept product ziv-aflibercept (Zaltrap®) is FDA-approved for cancer indications.

Ranibizumab (Lucentis®) is a recombinant humanized anti-VEGF antibody fragment that binds active forms of VEGF-A, thereby preventing the interaction of VEGF-A with its receptors and reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation. Ranibizumab was FDA-approved for treatment of neovascular (wet) AMD in 2006 and has subsequently been approved.
for treatment of macular edema following retinal vein occlusion and for
treatment of diabetic macular edema.

Bevacizumab (Avastin®) is a recombinant humanized anti-VEGF
antibody that is derived from the same murine monoclonal antibody
precursor as ranibizumab and binds to all isoforms of VEGF.
Bevacizumab is FDA-approved for a number of cancer indications, and
it is used off-label for treatment of neovascular conditions of the
choroid and retina.

Definitions:  

**Age-related macular degeneration (AMD):** A painless, progressive
deterioration of the macula, the central portion of the retina, that results
in loss of central vision needed for “straight ahead” tasks such as
reading, sewing, and driving. Late-stage AMD is classified as dry or
wet. The neovascular, exudative, wet form is due to choroidal
neovascularization, which leads to leakage of fluid, scarring, and vision
loss.

**Choroidal neovascularization:** The ingrowth of new vessels in the
sponge-like membrane in the eye located between the white outer
layer of the eye (sclera) and the retina.

**Macular edema:** Thickening and swelling of the macula due to
leakage of fluid into the retina that is caused by damage to the blood
vessels.

**Retina:** A layer of neural tissue at the back of eye that receives and
transmits visual signals. The macula is located at the center of the
retina and controls central vision.

**Retinal vein occlusion (RVO):** Blockage of central or branch retinal
veins due to a number of conditions including diabetic retinopathy,
hypertension, atherosclerosis, and some blood coagulation disorders.
Occlusion can cause leakage of fluid from the retinal veins resulting in
macular edema.

**Retinopathy:** Any disease process that damages the retinal tissue.

Policy:

I. **Pegaptanib (Macugen)**
   A. Intravitreal injections of pegaptanib may be considered
      **MEDICALLY NECESSARY** as a treatment of neovascular
      (wet) age-related macular degeneration.
   B. The use of pegaptanib for treatment of all other conditions is
      considered **INVESTIGATIVE.**

II. **Afiblercept (Eylea)**
   A. Intravitreal injections of afiblercept may be considered
      **MEDICALLY NECESSARY** for treatment of the following
      conditions:
      1. Neovascular (wet) age-related macular degeneration
      2. Macular edema following central retinal vein occlusion
B. The use of aflibercept for treatment of all other non-neoplastic conditions is considered INVESTIGATIVE.

III. Ranibizumab (Lucentis)
A. Intravitreal injections of ranibizumab may be considered MEDICALLY NECESSARY for treatment of the following conditions:
   1. Neovascular (wet) age-related macular degeneration
   2. Macular edema following retinal vein occlusion
   3. Diabetic macular edema
   4. Proliferative diabetic retinopathy as an adjunctive treatment to vitrectomy or photocoagulation
   5. Choroidal neovascularization due to angiod streaks, central serous chorioretinopathy, choroidal rupture or trauma, idiopathic choroidal neovascularization, multifocal choroiditis, pathologic myopia, presumed ocular histoplasmosis syndrome or uveitis
B. The use of ranibizumab for treatment of all other conditions is considered INVESTIGATIVE.

IV. Bevacizumab (Avastin)
A. Intravitreal injections of bevacizumab may be considered MEDICALLY NECESSARY for treatment of the following conditions:
   1. Neovascular (wet) age-related macular degeneration
   2. Macular edema following retinal vein occlusion
   3. Diabetic macular edema
   4. Proliferative diabetic retinopathy as an adjunctive treatment to vitrectomy or photocoagulation
   5. Choroidal neovascularization due to angiod streaks, central serous chorioretinopathy, choroidal rupture or trauma, idiopathic choroidal neovascularization, multifocal choroiditis, pathologic myopia, presumed ocular histoplasmosis syndrome, or uveitis
   6. Neovascular glaucoma
   7. Rubeosis (i.e., neovascularization of the iris)
   8. Retinopathy of prematurity
B. The use of bevacizumab for treatment of all other non-neoplastic conditions is considered INVESTIGATIVE.

Coverage: Blue Cross and Blue Shield of Minnesota medical policies apply generally to all Blue Cross and Blue Plus plans and products. Benefit plans vary in coverage and some plans may not provide coverage for certain services addressed in the medical policies.

Medicaid products and some self-insured plans may have additional policies and prior authorization requirements. Receipt of benefits is subject to all terms and conditions of the member’s summary plan description (SPD). As applicable, review the provisions relating to a specific coverage determination, including exclusions and limitations. Blue Cross reserves the right to revise, update and/or add to its
medical policies at any time without notice.

For Medicare NCD and/or Medicare LCD, please consult CMS or National Government Services websites.

Refer to the Pre-Certification/Pre-Authorization section of the Medical Behavioral Health Policy Manual for the full list of services, procedures, prescription drugs, and medical devices that require Pre-certification/Pre-Authorization. Note that services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial of claims may result if criteria are not met.

Coding: The following codes are included below for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

CPT:
67028 Intravitreal injection of a pharmacologic agent (separate procedure)

HCPCS:
J0178 Injection, aflibercept, 1 mg
J2503 Injection, pegaptanib sodium, 0.3mg
J2778 Injection, ranibizumab, 0.1 mg

Deleted Code: Q2046

Policy History: Developed September 13, 2006

Most recent history:
Revised September 8, 2010
Reviewed September 14, 2011
Revised October 10, 2012
Revised October 9, 2013

Cross Reference:

Current Procedural Terminology (CPT®) is copyright 2013 American Medical Association. All Rights Reserved. No fee schedules, basic units, relative values, or related listings are included in CPT. The AMA assumes no liability for the data contained herein. Applicable FARS/DFARS restrictions apply to government use.

Copyright 2014 Blue Cross Blue Shield of Minnesota.