Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

Effective Date: 02/08/2024

Aflibercept Products
Eylea® (aflibercept)
Eylea® HD (aflibercept)

HCPCS: Eylea: J0178; Eylea HD: J0177

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved indication
   b. FDA approved age
   c. Treatment with bevacizumab or a bevacizumab biosimilar has been ineffective, not tolerated or contraindicated
      i. Trial and failure of bevacizumab is NOT required for those with a diagnosis of diabetic macular edema when visual acuity in the affected eye(s) is less than or equal to 20/50
      ii. Trial and failure of bevacizumab is not required for those with a diagnosis of retinopathy of prematurity (ROP)
   d. Diagnosis of ROP
      i. Must have a maximal gestational age of 32 weeks OR a maximum birth weight of 1500 grams
      ii. Must weight greater than 800 grams on the day of treatment
      iii. Must have one of the following retinal findings classified according to the International Classification for Retinopathy of Prematurity in the treatment eye(s):
         a) ROP Zone I Stage 1+, 2+, 3 or 3+
         b) ROP Zone II Stage 2+ or 3+
         c) Aggressive posterior ROP
   e. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: For at least 60 days and up to one year at a time
   c. Renewal Criteria:
      i. ROP: Patient must meet criteria in subbullet A, d to be considered for retreatment
      ii. All other indications: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Intravitreal injections of anti-vascular endothelial growth factor (VEGF) have been widely used by ophthalmologists to treat a variety of ocular diseases. They are injected directly into the eye to prevent the formation of new blood vessels and reduce blood vessel leakage and inflammation. Eylea is currently approved to treat the following indications: diabetic macular edema (DME), diabetic retinopathy (DR), macular edema due to retinal vein occlusion (RVO), neovascular (wet) age related macular degeneration (AMD), and ROP. Eylea HD is currently approved for use in wet AMD, DME, and DR.

- Age-related Macular Degeneration

    - Age-related macular degeneration is a degenerative disease of the macula that results primarily in loss of central vision. Wet AMD is characterized by growth of abnormal vessels into the subretinal space. These abnormal blood vessels leak leading to collections of subretinal fluid and/or blood beneath the retina. The 2022 American Academy of Ophthalmologists (AAO) Age-Related Macular Degeneration Preferred Practice Pattern Guidelines recommend observation and early detection, antioxidant vitamin and mineral supplements, and intravitreal injections of anti-VEGF agents for the management of wet AMD. Guidelines recommend Eylea, Avastin®, Vabysmo™, or Lucentis® for treatment. The guidelines have not been updated with Beovu®, Byooviz™, and Susvimo™.

- Diabetic retinopathy and Diabetic Macular Edema

    - Diabetic retinopathy and DME are common complications and the ocular manifestations of end-organ damage in diabetes mellitus. The 2022 AAO Diabetic Retinopathy Preferred Practice Pattern Guidelines state the goals of therapy for DR and DME include improvement or stabilization of visual function, improvement in vision-related quality of life, and optimal control of blood glucose, blood pressure, and other metabolic risk factors. Patients should always be treated with anti-VEGF therapy if they have severe non-proliferative DR or proliferative DR with center-involved macular edema. In cases of mild to moderate non-proliferative DR with center-involved macular edema, patients should also receive intravitreal injections. The guidelines support the use of Lucentis, Eylea, Vabysmo, and Avastin. AAO recommendations were based on trials comparing Eylea, Avastin, and Lucentis to focal laser treatment. All trials showed that treatment with VEGF inhibitors resulted in statistically and clinically significant improvements in visual acuity in patients with DME after one to two years compared to laser treatment.

- Retinal Vein Occlusion

    - Retinal vein occlusion occurs when there is partial or complete obstruction of a retinal vein. Vision loss can occur with RVO and is associated with macular ischemia or edema, retinal hemorrhages, vitreous hemorrhage, or epiretinal membrane formation. The 2019 AAO Retinal Vein Occlusions Preferred Practice Pattern Guidelines recommend anti-VEGF therapy as first-line treatment for macular edema caused by RVO. The guidelines support the use of Lucentis, Eylea, and Avastin. The guidelines state VEGF inhibitors, Eylea, Avastin, and Lucentis, are more effective than sham injection or laser therapy in maintaining or improving visual acuity in patients with macular edema secondary to RVO.

- There are very few randomized control trials that assess the efficacy of one anti-VEGF therapy over another. Of the two that are available, Avastin, Eylea, and Lucentis were all shown to be non-inferior to each other, and because of this, choice of therapy should be based on patient characteristics, side effect profiles, cost, and availability. However, a 2015 study conducted by Wells, et al. did show Eylea was superior to Avastin therapy when patients had a visual acuity of less than or equal to 20/50. In addition, a subcohort analysis of the YOSEMITE AND RHINE trials showed Vabysmo demonstrated BCVA gains similar to aflibercept, while demonstrating numerically greater improvements in anatomic outcomes at years 1 and 2. Therefore, in these scenarios Avastin should not be used prior to Eylea or Vabysmo.

- Retinopathy of Prematurity

    - ROP is a developmental vascular proliferative disorder that occurs in the retina of preterm infants with incomplete retinal vascularization and is an important cause of severe visual impairment in childhood. There have been over 50 different risk factors identified for development of ROP. The most common are low birth weight and low gestational age. ROP typically begins approximately 34 weeks post-menstrual age (PMA), although it may be seen as early as 30 to 32 weeks. It advances irregularly until 40 to 45 weeks PMA but resolves spontaneously in the majority of infants. Ocular outcome is typically poor in infants with severe untreated ROP. Among untreated eyes, poor structural outcomes occurred in 3.1% of eyes, and poor Snellen visual acuity occurred in 5.1% of eyes.

    - Pathogenesis is thought to occur in two steps. First, an initial injury caused by factors such as hypotension, hypoxia, or hyperoxia, with free radical formation, injures newly developing blood vessels and disrupts normal angiogenesis. Following this disruption, vessels either resume normal growth or new vessels grow abnormally out from the retina into the vitreous. Increased permeability of these abnormal new vessels can result in retinal edema and hemorrhage. Abnormal fibrovascular tissue may develop along with the neovascularization and later contract, producing traction on the retina. In some severe cases, this results in retinal distortion or retinal detachment. However, in most instances, the abnormal vascular tissue regresses with little residual effect.

    - The International Classification for Retinopathy of Prematurity (ICROP) provides a uniform approach to documenting the extent and severity of disease. Four features are evaluated:

        - Zone: describes the disease location on the retinal surface in relation to the disc, from the central zone (I) to the outer crescent (zone III)

        - Stage: describes the severity from mildest disease (flat white line of demarcation (stage 1)) to most severe (total retinal detachment (stage 5))

        - Extent: described by dividing the retinal surface in 12 sections, similar to hours of a clock

        - Presence or absence of plus disease, the most important indicator of disease severity. Preplus disease is an intermediate state between normal posterior pole vessels and plus disease. Plus disease is characterized by abnormal dilation and tortuosity of the posterior pole vessels.

    - Treatment is initiated when the infant develops high-risk prethreshold ROP, also called type I ROP. Type I ROP is defined as any of the following:

        - Any stage ROP with plus disease in zone I

        - Stage 3 ROP without plus disease in zone I

- Stage 2 or 3 ROP with plus disease in zone II

- Treatment may consist of retinal ablative therapy with laser photocoagulation or intravitreal injection of an anti-VEGF agent. Eyelea is the only FDA approved anti-VEGF for the ROP although Avastin and Lucentis have also been used off-label for this patient population. The choice between the two treatment modalities is largely based on the experience and preference of the treating ophthalmologist and the preferences of the patient's caregiver. Treatment should be undertaken as soon as is practicable and, generally, should not be delayed beyond 72 hours following diagnosis.

- Approval of Eylea for ROP was based on data from two randomized, global, Phase III trials, FIREFLEYE (n = 113) and BUTTERFLEYE (n = 120), which compared Eylea to laser photocoagulation in infants with ROP. Patients had to have a maximum gestational age of 32 weeks or a maximum birth weight of 1500 grams. They also had to weigh greater than 800 grams on the day of treatment. Patients also had to meet criteria for type I ROP. Eylea did not meet the goal of noninferiority to laser treatment at 52 weeks in either trial, although about 80% of infants treated with Eylea achieved an absence of active ROP in each trial.

- For patients who fail to achieve ROP regression with the initial therapy and for those in whom vision-threatening ROP recurs, further therapy generally consists of a second treatment using either the same modality or a different modality. Some studies have reported recurrence in as many as one-quarter of treated patients. Reported recurrence rates vary considerably depending on the timing of treatment, the laser treatment technique, the specific anti-VEGF agent and dose used, and/or the definition used to identify recurrence. Patients should meet the type I RO definition to be considered for retreatment.

References:

1. Eylea [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; December 2023.
2. Eylea HD [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; December 2023.
3. Avastin [prescribing information]. South San Francisco, CA: Genentech, Inc.; January 2021.
4. Flaxel CJ, Adelman RA, Bailey ST, et al. Age-related macular degeneration preferred practice pattern. Ophthalmology. 2020 Jan (updated March 2022); 127 (1): P1 - P65.
5. Tufail A, Patel PJ, Egan C, et al. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomized double masked study. BMJ. 2010; 340: c2459.
6. Zhand H, Liu ZL, Sun P, et al. Intravitreal bevacizumab for treatment of macular edema secondary to central retinal vein occlusion: eighteen-month results of a prospective trial. J Ocul Pharmacol Ther. 2011 Dec; 27 (6): 615 - 21.
7. Ghanem AA, El- Kannishy AM, El- Wehidy AS, et al. Intravitreal bevacizumab (avastin) as an adjuvant treatment in cases of neovascular glaucoma. Middle East Afr J Ophthalmol. 2009; 16: 75 - 9.
8. Michaelides M, Kaines A, Hamilton R, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT Study). Amer Acad Ophth. 2010 Mar; 117 (6): 1078 – 86.
9. Korobelnik JF, Do D, Scmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. Ophthalmology. 2014 Nov; 121 (11): 2247 – 54.
10. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. NEJM. 2015 March 26; 372 (13): 1193 – 203.
11. Sarwar S, Clearfield E, Soliman MK, et al. Aflibercept for neovascular age-related macular degeneration. The Cochrane database of systematic reviews. 2016 Feb 8; 2: CD011346. PMID: 26857947.
12. Vedula SS & Krzystolik MG. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for neovascular age-related macular degeneration. The Cochrane database of systematic reviews. 2008(2):CD005139. PMID: 18425911 6.
13. Solomon SD, Lindsley K, Vedula SS, et al. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. The Cochrane database of systematic reviews. 2019 Mar 4; 3: CD005139. PMID: 30834517.

14. Flaxel CJ, Adelman RA, Bailey ST, et al. Diabetic retinopathy preferred practice pattern. Ophthalmology. 2020 Jan (March 2022); 127 (1): P66 - P145.
15. Flaxel CJ, Adelman RA, Bailey ST, et al. Retinal vein occlusions preferred practice pattern. Ophthalmology. 2019 Sept 25; 127 (2): 288 – 320.
16. Clinicaltrials.gov. Randomized, controlled, multi-center study to assess the efficacy, safety, and tolerability of intravitreal aflibercept compared to laser photocoagulation in patients with retinopathy of prematurity. Available at: https://clinicaltrials.gov/ct2/show/NCT04101721. Accessed on February 15, 2023.
17. Stahl A, Sukgen EA, Wu WC, et al. Effect of intravitreal aflibercept vs laser photocoagulation on treatment success of retinopathy of prematurity: the FIREFLEYE randomized clinical trial. JAMA. 2022 Jul 26; 328 (4): 348 - 59.
18. Good WV. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc. 2004; 102: 233 – 48.
19. Jhaveri CD, Glassman AR, Ferris FL, et al. Aflibercept monotherapy or bevacizumab first for diabetic macular edema. NEJM. 2022 Aug 25; 387: 692 – 703.
20. Clinicaltrials.gov. Randomized, double-masked, active-controlled, phase 3 study of the efficacy and safety of high dose aflibercept in patients with neovascular age-related macular degeneration (NCT04423718). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04423718. Accessed on August 22, 2023.
21. Clinicaltrials.gov. Study of a high-dose aflibercept in participants with diabetic eye disease (PHOTON) (NCT04429503). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04429503. Accessed on August 22, 2023.

Policy History		
#	Date	Change Description
1.9	Effective Date: 02/08/2024	Updated to remove the step through Vabysmo on Eylea HD for the Medicare line of business
1.8	Effective Date: 10/15/2023	UM medical management system update for MAPPO and BCNA for Eylea HD
1.7	Effective Date: 10/12/2023	Updated to add Eylea HD and a step through Eylea and/or Vabysmo prior to the use of Eylea HD when using every 8 week dosing for Medicare. The name of the policy was changed from Eylea to Aflibercept.
1.6	Effective Date: 09/07/2023	UM medical management system update for BCBS and BCN for Eylea HD
1.5	Effective Date: 08/10/2023	Updated to not require step through Byooviz for all indications
1.4	Effective Date: 06/08/2023	Updated to not require step through Byooviz for DME when vision is worse than 20/50
1.3	Effective Date: 04/06/2023	New policy. This policy replaces previously approved criteria that was embedded in the Intravitreal Injections for Retinal Conditions Policy which is being split into individual drug policies and retired. The authorization period was updated from up to 1 year to at least 60 days and up to 1 year, a step through Byooviz was added, and the indication for retinopathy of prematurity was added.
1.2	Effective Date: 01/01/2020	UM medical management system update for BCBS for Eylea
1.1	Effective Date: 07/05/2017	UM medical management system update for MAPPO and BCNA for Eylea
1.0	Effective Date: 11/08/2012	UM medical management system update for BCN for Eylea

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*

Blue Cross Blue Shield/Blue Care Network of Michigan
Medication Authorization Request Form
Aflibercept Products
Eylea® (aflibercept): J0178, Eylea HD (aflibercept): J3590

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

This form is to be used by participating physicians to obtain coverage for Eylea and Eylea HD. For commercial members only, please complete this form and submit via fax to 1-877-325-5979. If you have any questions regarding this process, please contact BCBSM Provider Relations and Servicing or the Medical Drug Helpdesk at 1-800-437-3803 for assistance.

PATIENT INFORMATION		PHYSICIAN INFORMATION
Name		**Name**
ID Number		**Specialty**
D.O.B.	☐Male ☐Female	**Address**
Diagnosis		**City /State/Zip**
Drug Name		**Phone/Fax: P**: ( ) - **F**: ( ) -
Dose and Quantity		**NPI**
Directions		**Contact Person**
Date of Service(s)		**Contact Person Phone / Ext.**

STEP 1: **DISEASE STATE INFORMATION**

1. Is this request for: ☐ Initiation ☐ Continuation *Date patient started therapy:* _____

2. Please provide the NPI number for the place of administration: _____

3. **Initiation AND Continuation of therapy:**
   a. What eye(s) will be treated? ☐ Left eye ☐ Right eye

   b. What is the patient's dose and frequency of requested medication?
   Initiation - Dose: _____mg Frequency: ☐ 4 weeks ☐ 6 weeks ☐ 8 weeks ☐ Other: _____
   Maintenance - Dose: _____mg Frequency every: ☐ 4 weeks ☐ 6 weeks ☐ 8 weeks ☐ Other: _____

   c. What is the patient's diagnosis?
   ☐ Neovascular (wet) age-related macular degeneration (AMD) ☐ Diabetic retinopathy (DR) ☐ Retinopathy of Prematurity (ROP- go to f)
   ☐ Macular edema due to retinal vein occlusion (RVO) ☐ Other, Please specify: _____
   ☐ Diabetic macular edema (DME)
      a. What is the visual acuity in the right eye? _____
      b. What is the visual acuity in the left eye? _____

   d. Has the patient tried Avastin or bevacizumab biosimilar intravitreal treatment?
   ☐ No
   ☐ Yes
      i. Which eye was treated? ☐ Left eye ☐ Right eye
      ii. Please enter number of Avastin or a bevacizumab biosimilar injections patient has received and in which eye? _____
      iii. What was the patient's frequency of Avastin or bevacizumab biosimilar? ☐ 4 weeks ☐ 6 weeks ☐ 8 weeks ☐ Other: _____
      iv. Date of the last three Avastin or a bevacizumab biosimilar injection: _____
      v. What was the patient's outcome while on Avastin or bevacizumab biosimilar therapy?
      ☐ Visual acuity improvement ☐ Reduction in edema ☐ Decrease in retinal thickness ☐ Condition remained the same
      ☐ Worsening in visual acuity ☐ Increased edema ☐ Increase in retinal thickness ☐ Persistent edema
      ☐ Intolerance to the medication: _____
      ☐ Other, Please list: _____

   e. Has the patient failed treatment with other anti–VEGF therapy? ☐ Yes ☐ No
      i. If yes, List what treatment(s) patient failed: _____

   f. Diagnosis of retinopathy of prematurity (ROP) only
      i. What is the patient's gestational age (weeks)? _____
      ii. What is the patient's birth weight (kg)?_____
      iii. What is the patient's current weight(kg)? _____
      iv. What is the patient's ROP classified as?
      ☐ ROP Zone I Stage 1+, 2+, 3 or 3+ ☐ ROP Zone II Stage 2+ or 3+
      ☐ Aggressive posterior ROP ☐ Other

4. **Continuation of therapy:**
   a. How has the patient's condition changed while on therapy?
   ☐ Improved; Please describe: _____
   ☐ Stable; Please describe: _____
   ☐ Worsened; Please describe: _____
   ☐ Other; Please describe: _____

Please add any other supporting medical information necessary for our review

Coverage will not be provided if the prescribing physician's signature and date are not reflected on this document.

☐ Request for expedited review: I certify that applying the standard review time frame may seriously jeopardize the life or health of the member or the member's ability to regain maximum function

Physician's Name **Physician Signature** **Date**

Step 2: Checklist	☐ Form Completely Filled Out ☐ Attached chart notes	☐ Pertinent test results
Step 3: Submit	**By Fax: BCBSM Specialty Pharmacy Mailbox 1-877-325-5979**	**By Mail: BCBSM Specialty Pharmacy Program P.O. Box 312320, Detroit, MI 48231-2320**