# Clinical Policy: Aflibercept (Eylea)

Reference Number: CP.PHAR.184
Effective Date: 03.01.16
Last Review Date: 05.22
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

**See Important Reminder at the end of this policy for important regulatory and legal information.**

## Description

Aflibercept (Eylea®) is a vascular endothelial growth factor (VEGF) inhibitor.

## FDA Approved Indication(s)

Eylea is indicated for the treatment of patients with:

- Neovascular (wet) age-related macular degeneration (AMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)

## Policy/Criteria

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

It is the policy of health plans affiliated with Centene Corporation® that Eylea is **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Ophthalmic Disease** (must meet all)**:**

1. Diagnosis of one of the following (a, b, c, or d):
   a. Neovascular (wet) AMD;
   b. Macular edema following RVO;
   c. DME;
   d. DR;
2. Prescribed by or in consultation with an ophthalmologist;
3. Age ≥ 18 years;
4. For all indications, except for DME in members with baseline best corrected visual acuity (BCVA) worse than 20/50: Failure of bevacizumab intravitreal solution, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for bevacizumab intravitreal solution. Requests for IV formulations of Avastin, Mvasi, and Zirabev will not be approved.*
5. Dose does not exceed:
   a. AMD: 2 mg (1 vial) every 4 weeks for the first 3 months, then every 8 weeks thereafter;
   b. DME and DR: 2 mg (1 vial) every 4 weeks for the first 5 injections, then every 8 weeks thereafter;
   c. RVO: 2 mg (1 vial) every 4 weeks.

**Approval duration: 6 months**

**B. Other diagnoses/indications** (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

## II. Continued Therapy

**A. Ophthalmic Disease** (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy as evidenced by one of the following (a, b, c, or d):
   a. Detained neovascularization;
   b. Improvement/stabilization in visual acuity;
   c. Maintenance of corrected visual acuity from prior treatment;
   d. Supportive findings from optical coherence tomography or fluorescein angiography;
3. If request is for a dose increase, new dose does not exceed:
   a. DME and DR: 2 mg (1 vial) every 8 weeks;
   b. RVO: 2 mg (1 vial) every 4 weeks;
   c. AMD: One of the following (i or ii):
      i. Dose does not exceed 2 mg (1 vial) every 8 weeks;
      ii. Member meets both of the following (a and b):
         a) Documentation supports evidence of continued disease activity;
         b) New dose does not exceed 2 mg (1 vial) every 4 weeks.

**Approval duration: 6 months**

**B. Other diagnoses/indications** (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

## III. Diagnoses/Indications for which coverage is NOT authorized:

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or or evidence of coverage documents.

## IV. Appendices/General Information

*Appendix A: Abbreviation/Acronym Key*

AMD: age-related macular degeneration
BCVA: best corrected visual acuity
DME: diabetic macular edema
DR: diabetic retinopathy
FDA: Food and Drug Administration
RVO: retinal vein occlusion
VEGF: vascular endothelial growth factor

*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| Bevacizumab (Avastin®) | **Neovascular (wet) AMD:** 1.25 to 2.5 mg administered by intravitreal injection every 4 weeks. | 2.5 mg/month |
| | **Macular edema secondary to RVO:** 1 mg to 2.5 mg administered by intravitreal injection every 4 weeks | 2.5 mg/month |
| | **DR:** 1.25 mg administered by intravitreal injection every 6 weeks | 1.25 mg/6 weeks |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| | **DME:**<br>1.25 mg administered by intravitreal injection every 6 weeks | 1.25 mg/6 weeks |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s):
  - Ocular or periocular infection
  - Active intraocular inflammation
  - Hypersensitivity
- Boxed warning(s): none reported

*Appendix D: General Information*

- In the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (VIEW)-1 trial, the difference in the number of patients who lost fewer than 15 letters at 52 weeks between Eylea every 8 weeks compared to Lucentis was 0.6% (95.1% CI -0.32, 4.4). In terms of the number of patients who gained at least 15 letters, the mean difference between Eylea every 8 weeks was 6.6% (95.1% CI -1.0, 14.1). There were no adverse events that were found to be significant from the Lucentis arm.
- In a trial comparing Eylea, Avastin and Lucentis, the Diabetic Retinopathy Clinical Research Network found in patients with diabetic macular edema that when the initial visual-acuity letter score was 78 to 69 (equivalent to approximately 20/32 to 20/40) (51% of participants), the mean improvement was 8.0 with Eylea, 7.5 with Avastin, and 8.3 with Lucentis ($p > 0.50$ for each pair wise comparison). When the initial letter score was less than 69 (approximately 20/50 or worse), the mean improvement was 18.9 with Eylea, 11.8 with Avastin, and 14.2 with Lucentis ($p < 0.001$ for Eylea vs. Avastin, $p = 0.003$ for Eylea vs. Lucentis, and $p = 0.21$ for Lucentis vs. Avastin).
- In clinical trials for the treatment of AMD, DME, and DR, additional efficacy was not demonstrated in most patients when Eylea was dosed every 4 weeks as a maintenance dose, compared to every 8 weeks. Maintenance dosing at every 8 weeks should be attempted before increasing the intravitreal injection frequency to every 4 weeks.

## V. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| AMD | 2 mg (1 vial) administered by intravitreal injection once a month for 3 months then 2 mg every 2 months<br><br>*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).* | 2 mg/month |

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| Macular edema following RVO | 2 mg (1 vial) administered by intravitreal injection once every 4 weeks (monthly) | 2 mg/month |
| DME, DR | 2 mg (1 vial) administered by intravitreal injection once a month for the first 5 injections, followed by 2 mg via intravitreal injection once every 2 months<br><br>*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).* | 2 mg/month |

## VI. Product Availability

Single-dose vial and pre-filled syringe for intravitreal injection: 2 mg/0.05 mL solution

## VII. References

1. Eylea Prescribing Information. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; March 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125387s069lbl.pdf. Accessed November 9, 2021.
2. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration. San Francisco, CA: American Academy of Ophthalmology; September 2019. Available at: www.aao.org/ppp. Accessed November 9, 2021.
3. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Retinal Vein Occlusions. San Francisco, CA: American Academy of Ophthalmology; September 2019. Available at: www.aao.org/ppp. Accessed November 9, 2021.
4. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy. San Francisco, CA: American Academy of Ophthalmology; September 2019. Available at: www.aao.org/ppp. Accessed November 9, 2021.
5. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015 Mar 26;372(13):1193-203. Doi: 10.1056/NEJMoa1414264.

## Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

| HCPCS Codes | Description |
|---|---|
| J0178 | Injection, aflibercept, 1 mg |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 1Q18 annual review: Policy combined for Medicaid and commercial lines of business For Medicaid: Added bevacizumab redirection except for members with baseline visual acuity worse than 20/50 due to clinical superiority of Eylea, Moved initial and continued therapy criterion "not used concomitantly with other VEGF therapies" to section III. Diagnoses/indications NOT authorized, Added specialist requirement, Removed criteria checking for contraindications (ocular infections) due to its ophthalmic nature and addition of specialist requirement, Added age limit following safety guidance endorsed by Medical Affairs; References reviewed and updated. | 11.23.17 | 02.18 |
| 1Q 2019 annual review: removed section III requirement against concurrent use with VEGF medications; reduced commercial approval durations from length of benefit to 6 months; references reviewed and updated. | 11.20.18 | 02.19 |
| Criteria added for new FDA indication: use in patients with diabetic retinopathy without diabetic macular edema; references reviewed and updated. | 06.25.19 | 11.19 |
| RT4: added newly approved pre-filled syringe dosage form. | 09.11.19 | |
| 1Q 2020 annual review: no significant changes; added requirement of less frequent dosing; references reviewed and updated. | 10.23.19 | 02.20 |
| Ad Hoc update: clarified redirection from bevacizumab to Avastin as compounding pharmacies often break standard Avastin vials into smaller dosages specifically for ophthalmic use and there is a temporary CPT code not currently available to biosimilars. | 10.01.20 | |
| 1Q 2021 annual review: no significant changes; converted HIM-Medical Benefit to HIM line of business; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated | 12.01.20 | 02.21 |
| Ad Hoc update: updated redirection to "bevacizumab intravitreal solution" given availability of generic bevacizumab intravitreal solution and considering goal was to minimize use of IV bevacizumab products, most notably biosimilars; converted redirection language to "must use" | 03.04.21 | |
| Ad Hoc update: clarified "best corrected" for visual acuity for redirection to bevacizumab. | 06.22.21 | |
| Ad Hoc update: converted redirection language from "must use" to "Failure of" bevacizumab intravitreal solution. | 08.03.21 | |
| 1Q 2022 annual review: no significant changes; references reviewed and updated. | 11.09.21 | 02.22 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Added legacy WellCare line of business (WCG.CP.PHAR.184 to be retired) and shortened approval durations from 12 months to 6 months. | 01.26.22 | 05.22 |
| Template changes applied to other diagnoses/indications and continued therapy section. | 10.03.22 | |

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

**Note: For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.