Clinical Policy: Aflibercept (Eylea, Eylea HD)

Reference Number: LA.PHAR.184
Effective Date: 09.18.21
Last Review Date: ~~06.02.23~~04.05.24 Coding Implications
Line of Business: Medicaid Revision Log

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

****Please note: This policy is for medical benefit****

Description
Aflibercept (Eylea®~~)~~®, Eylea® HD) 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~~nAMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Retinopathy of prematurity (ROP)

Eylea HD is indicated for the treatment of patients with:
- nAMD
- DME
- 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 Louisiana Healthcare Connections that Eylea ~~is~~and Eylea HD are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Adult Ophthalmic Diseases (must meet all)**:**

1. Diagnosis of one of the following (a, b, c, or d):
   ~~a. Neovascular (wet) AMD;~~
   a. nAMD;
   b. Macular edema following RVO~~;~~ and request is for Eylea®;
   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) 20/50 or worse: 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~~:~~ one of the following (a or b):
   a. ~~AMD~~For Eylea, one of the following (i, ii, or iii):
      ~~a.~~i. nAMD: 2 mg (1 vial) every 4 weeks for the first 3 months, then every 8 weeks thereafter;
      ~~b.~~ii. DME and DR: 2 mg (1 vial) every 4 weeks for the first 5 injections, then every 8 weeks thereafter;
      ~~c.~~iii. RVO: 2 mg (1 vial) every 4 weeks~~.~~;
   b. For Eylea HD, one of the following (i or ii):
      i. nAMD and DME: 8 mg (1 vial) every 4 weeks for the first 3 doses, followed by 8 mg (1 vial) every 8-16 weeks thereafter;
      ii. DR: 8 mg (1 vial) every 4 weeks for the first 3 doses, followed by 8 mg (1 vial) every 8-12 weeks thereafter.

Approval duration: 6 months

B. Retinopathy of Prematurity (must meet all):

1. Request is for Eylea;

~~1.~~2. Diagnosis of ROP with one of the following retinal findings (a, b, or c):
   a. Zone I stage 1+, 2+, 3, or 3+;
   b. Zone II stage 2+ or 3+;
   c. Aggressive posterior ROP (AP-ROP);

~~2.~~3. Prescribed by or in consultation with an ophthalmologist;

~~3.~~4. Member meets all of the following (a and b):
   a. Gestational age at birth ≤ 32 weeks OR birth weight ≤ 1,500 g;
   b. Body weight > 800 g on day of treatment initiation;

~~4.~~5. 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.~~6. Dose does not exceed 0.4 mg one time, followed by an optional second and third dose of 0.4 mg at least 10 days apart for the same eye.

Approval duration: 6 months (up to 3 doses per eye per lifetime)

C. 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 LA.PMN.255
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 LA.PMN.53

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II. Continued Therapy

A. Adult Ophthalmic Diseases (must meet all)**:**

1. Currently receiving medication via Louisiana Healthcare Connections benefit or member has previously met initial approval criteria;
1. 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;
2. If request is for a dose increase, new dose does not exceed~~:~~ one of the following (a or b):
   a. For Eylea, one of the following (i or ii):
   ~~a.~~ nAMD, DME and DR: ~~2 mg (1 vial) every 8 weeks;~~
   ~~b.~~i.RVO: ~~2 mg (1 vial) every 4 weeks;~~
   ~~c.~~i. ~~AMD:~~ One of the following (~~i~~1 or ~~ii~~2):
      ~~i.~~1) Dose does not exceed 2 mg (1 vial) every 8 weeks;
      ~~ii.~~2) Member meets both of the following (a and b):
         ~~1)~~a) Documentation supports evidence of continued disease activity;
         ~~2)~~b) New dose does not exceed 2 mg (1 vial) every 4 weeks~~.~~;
   ii. RVO: 2 mg (1 vial) every 4 weeks;
   b. For Eylea HD, one of the following (i or ii):
      i. nAMD and DME: One of the following (1 or 2):
         1) Dose does not exceed 8 mg (1 vial) every 16 weeks;
         2) Member meets both of the following (a and b):
            a) Documentation supports evidence of continued disease activity;
            b) New dose does not exceed 8 mg (1 vial) every 8 weeks;
      ii. DR: One of the following (1 or 2):
         1) Dose does not exceed 8 mg (1 vial) every 12 weeks;
         2) Member meets both of the following (a and b):
            a) Documentation supports evidence of continued disease activity;
            b) New dose does not exceed 8 mg (1 vial) every 8 weeks.

Approval duration: 6 months

B. Retinopathy of Prematurity

1. Reauthorization beyond the first three doses is not permitted. Member must meet initial approval criteria.

Approval duration: Not applicable

C. 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 LA.PMN.255

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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 LA.PMN.53

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 policy – LA.PMN.53 for Medicaid, or or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AMD: age-related macular degeneration
AP: aggressive posterior
BCVA: best corrected visual acuity
DME: diabetic macular edema
DR: diabetic retinopathy
FDA: Food and Drug Administration
nAMD: neovascular (wet) age-related macular degeneration
ROP: retinopathy of prematurity
RVO: retinal vein occlusion
VEGF: vascular endothelial growth factor

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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:**~~ **nAMD:** 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
	DME: 1.25 mg administered by intravitreal injection every 6 weeks	1.25 mg/6 weeks
	ROP: Varies depending treatment regimen (i.e., followed by vitrectomy, laser therapy)	Varies

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~~nAMD, 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.
- In Eylea HD PULSAR and PHOTON studies of patients with nAMD and DME, patients could be treated as frequently as every 8 weeks based on protocol-defined visual and anatomic criteria, starting at week 16. For both the every 12 week- and every 16 week-Eylea HD treated groups, treatments were shown to be non-inferior and clinically equivalent to Eylea 2mg every 8 week treatment with respect to the change in BCVA score at week 48 using the pre-specified non-inferiority margin of 4 letters.
- From the Eylea HD PHOTON study, DR data was derived to support FDA approval for continued dosing every 8 to 12 weeks following the first 3 doses. For this measure, the group that received Eylea HD every 12 weeks met the noninferiority margin of 10% in comparison to Eylea 2 mg every 8 weeks; however, the group that received Eylea HD every 16 weeks did not.

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
~~AMD~~aflibercept (Eylea)	nAMD	2 mg (1 vial) administered by intravitreal injection once a month for 3 months then 2 mg every 2 months *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
aflibercept (Eylea)	Macular edema following RVO	2 mg (1 vial) administered by intravitreal injection once every 4 weeks (monthly)	2 mg/month
aflibercept (Eylea)	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 *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
aflibercept (Eylea)	ROP	0.4 mg administered by intravitreal injection once, followed by an optional two additional doses spaced at least 10 days apart for the same eye.	0.4 mg/dose
aflibercept (Eylea HD)	nAMD, DME	8 mg administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg via intravitreal injection once every 8 to 16 weeks, +/- 1 week	0.8 mg/dose

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Drug Name	Indication	Dosing Regimen	Maximum Dose
aflibercept (Eylea HD)	DR	8 mg administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg via intravitreal injection once every 8 to 12 weeks, +/- 1 week	0.8 mg/dose

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VI. Product Availability

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

Drug Name	Availability
aflibercept (Eylea)	Single-dose vial and pre-filled syringe for intravitreal injection: 2 mg/0.05 mL solution
aflibercept (Eylea HD)	Single-dose vial for intravitreal injection: 8 mg/0.07 mL solution

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VII. References

1. Eylea Prescribing Information. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; February 2023 Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125387s069lbl.pdf. Accessed ~~March~~November 2, 2023.
2. Eylea HD Prescribing Information. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; February 2023 Available at: https://www.regeneron.com/downloads/eyleahd_fpi.pdf. Accessed November 2, 2023.
~~2.~~3. 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 ~~October 18, 2022~~November 2, 2023.
~~3.~~4. 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 ~~October 18, 2022~~November 2, 2023.
~~4.~~5. 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 ~~October 18, 2022~~November 2, 2023.
~~5.~~6. 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.
~~6.~~7. Walter M. Fierson, American Academy of Pediatrics section on Ophthalmology, American Academcy of Opthalmology, American Association for Pediatric Opthalmology and Strabismus, American Association of Certified Orthoptists, et al., Screening Examination of Premature Infants for Retinopathy of Prematurity. *Pediatrics* December 2018; 142 (6): e20183061. 10.1542/peds.2018-3061

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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
J0177	Injection, aflibercept hd, 1 mg

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Converted corporate to local policy.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	06.21	09.18.21
Clarified "best corrected" for visual acuity for redirection to bevacizumab. Converted redirection language from "must use" to "Failure of" bevacizumab intravitreal solution. References reviewed and updated.	04.22	06.08.22
Template changes applied to other diagnoses/indications and continued therapy section. Clarified initial criteria from "worse than" to state BCVA 20/50 "or worse"; added criteria for newly FDA-approved indication of ROP; references reviewed and updated. Added verbiage this policy is for medical benefit only.	06.02.23	10.05.23
Annual review; added new Eylea HD formulation; for macular edema following RVO and ROP indications, added criteria that request is for Eylea; for continued use of Eylea in DME and DR, added option for every 4 week dosing to align with nAMD; references reviewed and updated. Added HCPCS code [J0177].	04.05.24	

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. LHCC 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.

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 LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. 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. LHCC 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.

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