Utilization Review Policy 267

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Eylea
- Eylea® (aflibercept for intravitreal injection – Regeneron)
- Eylea® HD (aflibercept intravitreal injection – Regeneron)

EFFECTIVE DATE: 1/1/2022
LAST REVISION DATE: 01/06/2025, 03/05/2026

COVERAGE CRITERIA FOR: All Aspirus Medicare Plans

OVERVIEW

Aflibercept is a vascular endothelial growth factor (VEGF) inhibitor.[1-3] Ophthalmic aflibercept products, Eylea, Eylea HD, and Pavblu, are given intravitreally for the treatment of ophthalmic conditions. Pavblu is a biosimilar to Eylea.[3]

Eylea and Pavblu are indicated for the following uses:[1-3]
- **Diabetic macular edema**.
- **Diabetic retinopathy**.
- **Macular edema following retinal vein occlusion**.
- **Neovascular (wet) age-related macular degeneration**.

Eylea is also indicated for the treatment of **retinopathy of prematurity**.[1]

Eylea HD, a high dose aflibercept product, is indicated for the following uses:[6]
- **Diabetic macular edema**.
- **Diabetic retinopathy**.
- **Neovascular (wet) age-related macular degeneration**.

Dosing Information:

The recommended dosing for Eylea and Pavblu for each indication is as follows:
- Diabetic macular edema or Diabetic retinopathy: 2 mg via intravitreal injection once every 4 weeks (approximately every 28 days, monthly) for the first five injections, followed by 2 mg once every 8 weeks (2 months). Although Eylea/Pavblu may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when Eylea/Pavblu 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).
- Macular edema following retinal vein occlusion: 2 mg via intravitreal injection once every 4 weeks (approximately every 25 days, monthly).
- Neovascular (wet) age-related macular degeneration: 2 mg via intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg every 8 weeks (2 months). Although Eylea/Pavblu may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not

demonstrated in most patients when Eylea/Pavblu was dosed every 4 weeks compared with every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy.

- Retinopathy of prematurity (Eylea only): 0.4 mg via intravitreal injection. Treatment is initiated with a single injection per eligible eye and may be given bilaterally on the same day. Injections may be repeated in each eye; treatment interval between doses injected into the same eye should be at least 10 days.

The recommended dosing for Eylea HD for each indication is as follows:

- Diabetic macular edema: 8 mg via intravitreal injection every 4 weeks (approximately every 28 days, +/- 7 days) for the first three doses, followed by 8 mg once every 8 to 16 weeks, +/- 1 week.
- Diabetic retinopathy: 8 mg via intravitreal injection every 4 weeks (approximately every 28 days, +/- 7 days) for the first three doses, followed by 8 mg once every 8 to 12 weeks, +/- 1 week.
- Neovascular (wet) age-related macular degeneration: 8 mg via intravitreal injection every 4 weeks (approximately every 28 days, +/- 7 days) for the first three doses, followed by 8 mg once every 8 to 16 weeks, +/- 1 week.

Other Uses with Supportive Evidence for Eylea and Pavblu

Overproduction of VEGF may lead to other eye conditions, including neovascular glaucoma and other retinal and choroidal neovascular conditions affecting the eye.[4,5] The VEGF inhibitors have the potential to be used off-label to reduce or slow visual impairment or vision loss associated with other eye conditions related to increased VEGF production.[4,6,7] The use of VEGF inhibitors have been shown to stop the angiogenic process, maintain visual acuity, and improve vision in patients with certain neovascular ophthalmic conditions. Therefore, research is rapidly evolving on the use of VEGF inhibitors in other neovascular ophthalmic conditions that threaten vision.[6,7]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of the intravitreal aflibercept products (Eylea, Eylea HD, and Pavblu). Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. All approvals are provided for the duration noted below.

This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the

absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage.

Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles.

Indications with a ^ below are also covered (and, if applicable, further detailed/referenced) in the corresponding Commercial Care Continuum (CC) Policy. Note: Additional criteria requirements for coverage of the same indication as outlined in the Commercial CC Policy and this Medicare Advantage CC Policy may NOT be the same.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Eylea, Eylea HD and Pavblu is recommended for requests meeting both the step therapy requirements and indication requirements:

Step Therapy Requirements (New Starts Only)

Criteria. *The patient must meet the following criteria (A, B, C, D, or E):*

A) For patients new to Eylea, Eylea HD or Pavblu therapy only, must have a trial of repackaged Avastin prior to approval of Eylea, Eylea HD or Pavblu. New starts to therapy defined as no use of Eylea, Eylea HD or Pavblu within the past 365 days for Medicare patients and includes use in either eye.

B) Patient has diabetic macular edema and has a baseline visual acuity worse than 20/40 according to the prescriber

C) Patient has diabetic macular edema with significant retinal thickening according to the prescriber;

D) Patient has diabetic retinopathy (without diabetic macular edema)

E) Patient has a contraindication or other clinical reason why repackaged Avastin cannot be tried before Eylea, Eylea HD or Pavblu.

Note: Step therapy only required for indications compendia supported for both Eylea, Eylea HD or Pavblu and Avastin.

FDA-Approved Indications

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1. Neovascular (Wet) Age-Related Macular Degeneration. ^

Criteria. Approve for 1 year.

Dosing. Approve if the requested dosing meets the following (A and B):

A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND

B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

2. Macular Edema Following Retinal Vein Occlusion. ^

Criteria. Approve for 1 year.

Dosing. Approve if the dose meets both criteria (A and B):
A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

3. Diabetic Macular Edema. ^

Criteria. Approve for 1 year.

Dosing. Approve if the dose meets both criteria (A and B):
A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

4. Diabetic Retinopathy. ^

Criteria. Approve for 1 year.

Dosing. Approve if the dose meets both criteria (A and B):
A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

5. Retinopathy of Prematurity. ^

Criteria. Approve for 1 year.

Dosing. Approve if the dose meets both of the following criteria (A and B):
A) The dose is 0.4 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 10 days for each eye being treated.

Other Uses with Supportive Evidence

6. Other Neovascular Diseases of the Eye . ^
Note: Examples of other neovascular diseases of the eye include angioid streaks, iris neovascularization, neovascular glaucoma, pachychoroid neovasculopathy, polypoidal choroidal vasculopathy, and presumed ocular histoplasmosis syndrome.

Criteria. Approve for 1 year.

Dosing. Approve if the dose meets both criteria (A and B):

A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

I. Coverage of Eylea HD is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Diabetic Macular Edema.** ^

Criteria. Approve for 1 year.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 8 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 21 days for each eye being treated.
Note: The recommended regimen is one dose every 4 weeks (approximately every 28 days +/- 7 day) for the first three doses, followed by one dose every 8 to 16 weeks, +/- 1 week. Some patients may benefit from every 4-week dosing (approximately every 28 days +/- 7 days).

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2. Diabetic Retinopathy. ^

Criteria. Approve for 1 year.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 8 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 21 days for each eye being treated.
Note: The recommended regimen is one dose every 4 weeks (approximately every 28 days +/- 7 day) for the first three doses, followed by one dose every 8 to 12 weeks, +/- 1 week. Some patients may benefit from every 4-week dosing (approximately every 28 days +/- 7 days).

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3. Macular Edema Following Retinal Vein Occlusion. ^

Criteria. Approve for 1 year.

Dosing. Approve if the dose meets BOTH of the following (A and B):

A) The dose is 8 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 21 days for each eye being treated.
Note: The recommended regimen is one dose every 4 weeks (approximately every 28 days +/- 7 day) for the first three to five doses, followed by one dose every 8 weeks, +/- 1 week. Some patients may benefit from every 4-week dosing (approximately every 28 days +/- 7 days.

4. Neovascular (Wet) Age-Related Macular Degeneration. ^

Criteria. Approve for 1 year.

Dosing. Approve if the dose meets both of the following (A and B):

A) The dose is 8 mg administered by intravitreal injection for each eye being treated; AND

B) The dosing interval is not more frequent than once every 21 days for each eye being treated.
Note: The recommended regimen is one dose every 4 weeks (approximately every 28 days +/- 7 day) for the first three doses, followed by one dose every 8 to 16 weeks, +/- 1 week. Some patients may benefit from every 4-week dosing (approximately every 28 days +/- 7 days).

Other Uses with Supportive Evidence

5. Other Neovascular Diseases of the Eye . ^

Criteria. Approve for 1 year.
Note: Examples of other neovascular diseases of the eye include angioid streaks, iris neovascularization, neovascular glaucoma, pachychoroid neovasculopathy, polypoidal choroidal vasculopathy, and presumed ocular histoplasmosis syndrome.

Dosing. Approve if the dose meets BOTH of the following (A and B):

A) The dose is 8 mg administered by intravitreal injection for each eye being treated; AND

B) The dosing interval is not more frequent than once every 21 days for each eye being treated

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of the intravitreal aflibercept products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Eylea® intravitreal injection [prescribing information]. Tarrytown, NY: Regeneron; December 2023.
2. Eylea® HD intravitreal injection [prescribing information]. Tarrytown, NY: Regeneron; December 2023.
3. Pavblu™ intravitreal injection [prescribing information]. Thousand Oaks, CA: Amgen; August 2024.
4. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs*. 2009;18(5):637-646.
5. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
6. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
7. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.
8. Centers for Medicare and Medicaid Services, National Government Services, Inc, Local Coverage Determination (LCD): Drugs and Biologicals, Coverage of, for Label and Off-Label Uses (L33394) [original date 10/01/2015; revision effective date 8/1/24]. Accessed December 2, 2024.

9. Centers for Medicare and Medicaid Services, National Government Services, Inc, Local Coverage Article (LCA): Billing and Coding: Ranibizumab, Aflibercept and Brolucizumab-dbll (A52451) [original date 10/01/2015; revision effective date 9/1/24]. Accessed December 2, 2024.

HISTORY

Type of Revision	Summary of Changes*	Date
Policy created	New Medicare Advantage Medical Policy	07/11/2018
Policy revision	Added Macugen to policy	11/05/2018
Policy revision	Reviewed and revised original policy created 07/11/2018 in accordance with Local Coverage Article A52451 and Ophthalmology – Vascular Endothelial Growth Factor (VEGF) Inhibitor Injectables Utilization Review Policy.	5/22/2019
Policy revision	Reviewed and revised original policy created 07/11/2018 in accordance with Local Coverage Determination L33394 and Ophthalmology – Vascular Endothelial Growth Factor Inhibitors - Eylea Utilization Review Policy.	11/06/2019
Policy revision	Non-clinical update to policy to add the statement "This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage."	1/30/2020
Policy revision	*Added the following to the Policy Statement "Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles." *Updated references	08/07/2020
Policy revision	**Diabetic Macular Edema, Diabetic Retinopathy, Macular Edema following Retinal Vein Occlusion,** and **Neovascular (wet) Aage-Related Macular Degeneration:** To align with the FDA-approved dosing, the dose was changed from "≤ 2 mg" to "is 2 mg". **Other Neovascular Diseases of the Eye:** Examples of other neovascular diseases of the eye were moved to a Note. To align with the FDA-approved dosing, the dose was changed from "≤ 2 mg" to "is 2 mg".	12/20/2021
Policy revision	**Retinopathy of Prematurity:** This condition was moved to the FDA-Approved Indications; previously, it was included in the Note of examples of Other Neovascular Diseases of the Eye, under "Other Uses with Supportive Evidence". For this indication, the dosing was	03/08/2023

	changed to be 0.4 mg administered per injection, with the dosing interval changed to be not more frequent than once every 10 days for each eye being treated (previously, it was the same as Other Neovascular Diseases of the Eye, which was 2 mg per treated eye, with a dosing interval of at least 25 days between doses).	
Policy revision	**Eylea HD:** Eylea HD was added to the policy; conditions and criteria for approval were added to the policy.	09/26/2023
Aspirus P&T Review	Policy reviewed and approved by Aspirus P&T committee. Annual review process	09/16/2024
Policy revision	**Pavblu:** Pavblu (biosimilar to Eylea) was added to the policy; conditions and criteria for approval for Pavblu are identical to those for Eylea. **Policy name:** Policy name was changed from Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Eylea and Eylea HD to Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Aflibercept Products.	01/06/2025
Aspirus P&T Review	Policy reviewed and approved by Aspirus P&T committee. Annual review process	09/15/2025
Selected revision	**Eylea: Other Uses with Supportive Evidence.** Other Neovascular Diseases of the Eye. The Note of examples of other neovascular diseases was revised to remove sickle cell neovascularization and choroidal neovascular conditions and the following examples were added: angioid streaks, iris neovascularization, pachychoroid neovasculopathy, polypoidal choroidal vasculopathy, and presumed ocular histoplasmosis. **Eylea HD: Other Uses with Supportive Evidence.** Added **"**Other Neovascular Diseases of the Eye" as a condition of approval. **Eylea HD, Macular Edema Following Retinal Vein Occlusion:** This condition of approval was added to the policy. Dosing recommendation for this condition was also added. **Eylea HD, Dosing section was revised to align with the updated Eylea HD prescribing information (PI).** **Diabetic Macular Edema:** The dosing interval was revised to read "not more frequent than once every 21 days for each eye being treated"; previously the dosing interval was "not more frequent than once every 21 days for the first three doses, followed by not more frequent that once every 7 weeks for each eye being treated". The revised PI notes that some patients may benefit from every 4-week dosing (approximately every 28 days, +/- 7 days). **Diabetic Retinopathy:** The dosing interval was revised to read "not more frequent than once every 21 days for each eye being treated"; previously the dosing interval was "not more frequent than once every 21 days for the first three doses, followed by not more frequent that once every 7 weeks for each eye being treated". The revised PI notes that some patients may benefit from every 4-week dosing (approximately every 28 days, +/- 7 days). **Neovascular (Wet) Age-Related Macular Degeneration:** The dosing interval was revised to read "not more frequent than once every 21 days for each eye being treated"; previously the dosing interval was "not more frequent than once every 21 days for the first three doses, followed by not more frequent that once every 7 weeks for each eye being treated". The revised PI notes that some patients may benefit from every 4-week dosing (approximately every 28 days, +/- 7 days).	03/05/2026