Effective Date **3/15/2025**
Coverage Policy Number **IP0540**

Aflibercept

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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for the following aflibercept products:

- **Eylea®** (aflibercept intravitreal injection)
- **Eylea® HD** (aflibercept intravitreal injection)
- **Pavblu™** (aflibercept-ayyh intravitreal injection)

Medical Necessity Criteria

Aflibercept products (Eylea, Eylea HD, and Pavblu) are considered medically necessary when ONE of the following are met:

I. **Aflibercept (Eylea and Pavblu).** Individual meets **ALL** of the following criteria:

1. Treatment of **ONE** of the following

A. Diabetic Macular Edema (DME)
B. Diabetic Retinopathy (DR)
C. Macular Edema following retinal vein occlusion (RVO)
D. Neovascular (wet) Age-Related Macular Degeneration
E. Retinopathy of Prematurity
F. Other Neovascular Diseases of the Eye (for example, neovascular glaucoma, sickle cell neovascularization, choroidal neovascular conditions)

2. Medication is prescribed by, or under the supervision of, an ophthalmologist
3. Preferred product criteria is met for the products as listed in the below tables

Dosing. ONE of the following dosing regimens:

1. For ALL covered diagnoses (except retinopathy of prematurity), **BOTH** of the following:
   A. 2 mg administered by intravitreal injection for each eye being treated
   B. The dosing interval is not more frequent than once every 25 days for each eye being treated
2. For retinopathy of prematurity, **BOTH** of the following:
   A. 0.4 mg administered by intravitreal injection for each eye being treated
   B. The dosing interval is not more frequent than once every 10 days for each eye being treated

II. **Aflibercept (Eylea HD).** Individual meets **ALL** of the following criteria:

1. Treatment of **ONE** of the following
   A. Diabetic Macular Edema (DME)
   B. Diabetic Retinopathy (DR)
   C. Neovascular (wet) Age-Related Macular Degeneration
2. Medication is prescribed by, or under the supervision of, an ophthalmologist
3. Preferred product criteria is met for the product as listed in the below tables

Dosing. For ALL covered diagnoses, **BOTH** of the following:

1. 8 mg administered by intravitreal injection for each eye being treated
2. The dosing interval is not more frequent than once every 21 days for three doses, followed by not more frequent than once every 7 weeks for each eye being treated

Employer Plans:

Product	Criteria
Eylea (aflibercept intravitreal injection)	**Eylea** is considered medically necessary when there is documentation of **ONE** of the following: 1. Currently receiving Eylea 2. **ONE** of the following: A. Failure, contraindication, or intolerance to repackaged bevacizumab B. If, in the professional opinion of the prescriber, the safety of using the repackaged bevacizumab or the supplier of the repackaged bevacizumab is of significant concern 3. According to the prescriber, patient has diabetic macular edema and a baseline Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) of 20/50 or worse (< 69 ETDRS letters) 4. Diabetic macular edema with significant retinal thickening 5. Diabetic retinopathy (without diabetic macular edema)
Eylea HD (aflibercept intravitreal injection)	**Eylea HD** is considered medically necessary when there is documentation of **ONE** of the following: 1. Currently receiving Eylea HD 2. **ONE** of the following:

Product	Criteria
	A. Failure, contraindication, or intolerance to repackaged bevacizumab B. If, in the professional opinion of the prescriber, the safety of using the repackaged bevacizumab or the supplier of the repackaged bevacizumab is of significant concern 3. According to the prescriber, patient has diabetic macular edema and a baseline Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) of 20/50 or worse (< 69 ETDRS letters) 4. Diabetic macular edema with significant retinal thickening 5. Diabetic retinopathy (without diabetic macular edema)
Pavblu (aflibercept-ayyh intravitreal injection)	**Pavblu** is considered medically necessary when there is documentation of **ONE** of the following: 1. Currently receiving Pavblu 2. **ONE** of the following: A. Failure, contraindication, or intolerance to repackaged bevacizumab B. If, in the professional opinion of the prescriber, the safety of using the repackaged bevacizumab or the supplier of the repackaged bevacizumab is of significant concern 3. According to the prescriber, patient has diabetic macular edema and a baseline Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) of 20/50 or worse (< 69 ETDRS letters) 4. Diabetic macular edema with significant retinal thickening 5. Diabetic retinopathy (without diabetic macular edema)

Individual and Family Plans:

Product	Criteria
Eylea (aflibercept intravitreal injection)	**Eylea** is considered medically necessary when there is documentation of **ONE** of the following: 1. Currently receiving Eylea 2. **ONE** of the following: A. Failure, contraindication, or intolerance to repackaged bevacizumab B. If, in the professional opinion of the prescriber, the safety of using the repackaged bevacizumab or the supplier of the repackaged bevacizumab is of significant concern 3. According to the prescriber, patient has diabetic macular edema and a baseline Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) of 20/50 or worse (< 69 ETDRS letters) 4. Diabetic macular edema with significant retinal thickening 5. Diabetic retinopathy (without diabetic macular edema)
Eylea HD (aflibercept intravitreal injection)	**Eylea HD** is considered medically necessary when there is documentation of **ONE** of the following: 1. Currently receiving Eylea HD 2. **ONE** of the following: A. Failure, contraindication, or intolerance to repackaged bevacizumab B. If, in the professional opinion of the prescriber, the safety of using the repackaged bevacizumab or the supplier of the repackaged bevacizumab is of significant concern 3. According to the prescriber, patient has diabetic macular edema and a baseline Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) of 20/50 or worse (< 69 ETDRS letters)

Product	Criteria
	4. Diabetic macular edema with significant retinal thickening 5. Diabetic retinopathy (without diabetic macular edema)
Pavblu (aflibercept-ayyh intravitreal injection)	**Pavblu** is considered medically necessary when there is documentation of **ONE** of the following: 1. Currently receiving Pavblu 2. **ONE** of the following: A. Failure, contraindication, or intolerance to repackaged bevacizumab B. If, in the professional opinion of the prescriber, the safety of using the repackaged bevacizumab or the supplier of the repackaged bevacizumab is of significant concern 3. According to the prescriber, patient has diabetic macular edema and a baseline Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) of 20/50 or worse (< 69 ETDRS letters) 4. Diabetic macular edema with significant retinal thickening 5. Diabetic retinopathy (without diabetic macular edema)

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Continuation of aflibercept (Eylea, Eylea HD, and Pavblu) is considered medically necessary for ALL covered diagnoses when the above medical necessity criteria are met AND beneficial response is demonstrated.

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven.

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
C9399	Unclassified drugs or biologicals (Code effective until 3/31/2025)
J0177	Injection, aflibercept HD, 1 mg (Code effective 4/1/2024)
J0178	Injection, aflibercept, 1 mg
J3490	Unclassified drugs (Code effective until 3/31/2025)

HCPCS Codes	Description
J3590	Unclassified biologics (Code effective until 3/31/2025)
Q5147	Injection, aflibercept-ayyh (pavblu), biosimilar, 1 mg (Code effective 4/1/2025)

Background

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]

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.

Revision Details

Type of Revision	Summary of Changes	Date
Selected Revision	**Updated** review date, disclaimer, refreshed background, and references, and added change history. **Eylea, Eylea HD:** For the exclusion criterion "Patient has diabetic macular edema and a baseline visual acuity worse than 20/40", the threshold was rephrased as "20/50 or worse (< 69 Early Treatment Diabetic Retinopathy Study [ETDRS] letters)" to align with the language used in the study. In addition, baseline visual acuity was clarified as "ETDRS best-corrected visual acuity (BCVA)." **Updated Coding:** **Removed** J3590 **Added** J0177 (effective 4/1/2024)	12/1/2024
Selected Revision	**Pavblu:** Pavblu (biosimilar to Eylea) was added to the policy; conditions and criteria for approval for Pavblu are identical to those for Eylea. **Preferred Product Table:** **Updated** criteria **from** "Diabetic retinopathy **to** "Diabetic retinopathy (without diabetic macular edema) for Eylea and Eylea HD." **Added** preferred product step requirement for Pavblu. **Updated HCPCS Coding:** **Added:** C9399, J3490, J3590	2/1/2025
Selected Revision	**Updated HCPCS Coding**	3/15/2025

	Added new code Q5147 that will be effective on 4/1/2025 **Added** that C9399, J3490 & J3590 will be effective until 3/31/2025	

The policy effective date is in force until updated or retired.