

**Pegcetacoplan (SYFOVRE) Intravitreal Injection
National Drug Monograph
January 2024**

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Pegcetacoplan is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).
- There are 3 stages of AMD: early, intermediate, and late. In the late stage, there are 2 major forms; dry (non-neovascular) and wet (neovascular, exudative). Geographic atrophy is the advanced late stage of dry AMD.
- While vascular endothelial growth factor is the driver for the growth of neovascularization in nAMD, activation of the complement cascade is one of the main pathways involved in progression of dry AMD.
- With aging, oxidative damage resulting from exposure to intrinsic, extrinsic, and environmental stressors can result in the formation of drusen, yellow deposits of lipids between the retinal pigment epithelium (RPE) and Bruch's membrane (early to intermediate AMD)
- Drusen accumulation may trigger chronic inflammation via multiple pathways including the complement cascade
- Chronic inflammation can eventually lead to photoreceptor, RPE, and choriocapillaris cell death causing the appearance of sharply defined atrophic lesions and can progress to irreversible visual function loss.
- Lesions usually first appear in the nonfoveal (or extrafoveal) region of the macula and progress over time to the central fovea (subfoveal)
- Extrafoveal lesions affect visual performance, such as reading, driving, and low-light vision. Foveal lesions affect central visual acuity.
- The complement cascade has 3 complement activation pathways (classical, alternative, and lectin). C3 is the point of convergence for all 3 activation pathways and is upstream of all major effectors of complement activation.
- Pegcetacoplan binds to complement protein C3 and its activation fragment C3b with high affinity thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation.

Dosage Form(s) Under Review

- Injection: 150 mg/mL in a single-dose vial
- The recommended dose is 15 mg (0.1 mL of 150 mg/mL solution) administered by intravitreal injection to each affected eye once every 25 to 60 days

Clinical Evidence Summary

Efficacy Considerations

Two phase 3, randomized, double-blind 24-months studies, DERBY (n=621) and OAKS (n=637), compared the efficacy and safety of pegcetacoplan with sham in patients with GA (atrophic nonexudative age-related macular degeneration), with or without subfoveal involvement, secondary to AMD. Patients were randomized 2:2:1:1 to

Pegcetacoplan Monograph

pegcetacoplan 15mg every month, pegcetacoplan 15mg every other month, sham every month, and sham every other month.

The primary outcome was change in the total area of GA lesions from baseline as measured by fundus autofluorescence at 12 months. Patients continued to receive masked treatment for 24 months.

- Key inclusion criteria: Age \geq 60 years; best-corrected visual acuity (BCVA) \geq 24 letters; diagnosis of GA of macula secondary to AMD confirmed by the reading center; total GA lesion area \geq 2.5 and \leq 17.5 mm²; If GA is multifocal, at least one focal lesion must be \geq 1.25 mm² on fundus autofluorescence (FAF) imaging; lesions may be nonsubfoveal or subfoveal
- Key exclusion criteria: GA secondary to a condition other than AMD; history of or active choroidal neovascularization (CNV) in the study eye, associated with AMD or any other cause, including any evidence of retinal pigment epithelium tear or evidence of neovascularization anywhere (CNV in fellow eye was not an exclusion criterion)
- Baseline characteristic (OAKS and DERBY):
 - Mean age 78.7 years; males 39%; White 93%; study site USA 68%
 - Mean GA lesion size 8.23mm² (OAKS) and 8.29mm² (DERBY); GA lesion size <7.5mm² 49%
 - Mean square root GA lesion size: 2.79mm
 - Subfoveal lesions 63%; nonsubfoveal lesions 37%; unifocal lesion 30%
 - Bilateral GA 81% (obtained from FDA review)
 - > 20 intermediate/large drusen: 49% (OAKS) and 43% (DERBY)
 - Mean BCVA 59 letters, mean low-luminance deficit 26 letters
 - Active or history of CNV in fellow eye 20%
- Results:
 - Combined results of OAKS and DERBY show that pegcetacoplan administered monthly or every other month reduced the growth of GA lesions compared to sham by 16% (monthly) and 14% (EOM) at month 12 and by 21% (monthly) and 17% (EOM) at monthly 24. Results for individual trials are shown in Table 1. It should be noted that in DERBY, the changes were not significant at month 12.
 - The greatest effect occurred during months 18-24 (see product labeling or publication for results at 0-6, 6-12, 12-18, and 18-24 months)
 - Mean number of injections received over 24 months was 18.8 (monthly), 10.1 (EOM), 14.5 (sham pooled-includes monthly and EOM)
 - Compared to sham treatment, the reduction in lesion growth was greater for nonsubfoveal lesions (26% monthly; 22% every other month) than subfoveal lesions (19% monthly; 16% every other month) in the combined studies at month 24.
 - There were no statistically significant differences across study arms on key secondary endpoints at 24 months for BCVA, monocular maximum reading speed, Functional Reading Independence Index, National Eye Institute Visual Functioning Questionnaire 25 distance activity subscale score (NEI VFQ-25), and microperimetry: mean threshold sensitivity (OAKS only).
 - Exploratory post hoc analysis of OAKS and DERBY at 12 months using artificial intelligence-based automated segmentation to map photoreceptor and RPE layers showed
 - Reduction in loss of photoreceptors compared to sham: OAKS (75% monthly; 47% every other month) and DERBY (77% monthly; 61% (every other month)
 - Reduction in loss of RPE compared to sham: OAKS (20% monthly; 15% every other month) and DERBY (36% monthly; 20% (every other month)

Table 1: Change in GA Lesion Area

		OAKS			DERBY		
		PEG monthly (n=202)	PEG EOM (n=205)	Sham (n=207)	PEG monthly (n=201)	PEG EOM (n=201)	Sham (n=195)
12 months	LSM change from BL (mm ²)	1.56	1.65	1.97	1.73	1.76	1.96
	Absolute diff (95%CI) PEG vs. sham	-0.41 (-0.64, -0.18)	-0.32 (-0.54, -0.09)	NA	-0.23** (-0.47, 0.01)	-0.21** (-0.44, 0.03)	NA
	Percent Difference from sham	-21%	-16%	NA	-12%	-11%	NA
24 months	LSM change from BL (mm ²)	3.11	3.26	3.98	3.28	3.31	4.00
	Absolute diff (95%CI) PEG vs. sham	-0.87 (-1.27, -0.47)	-0.72 (-1.10, -0.33)	NA	-0.73 (-1.14, -0.31)	-0.70 (-1.11, -0.28)	NA
	Percent Difference from sham	-22%	-18%	NA	-18%	-17%	NA

Abbreviations: BL=baseline; EOM=every other month; GA=geographic atrophy; LSM=least square mean; PEG=pegcetacoplan
Results shown as non-transformed GA growth slope analysis (mm²)

**In DERBY, change versus sham was not statistically significant

Safety Considerations

- **Boxed warnings:** None

- **Contraindications:**

- Ocular or periocular infection
- Active Intraocular Inflammation

- **Post-Marketing experience:**

Between April 25, 2023 and October 12, 2023, the American Society of Retina Specialists had received reports of retinal vasculitis in 14 eyes (11 occlusive retinal vasculopathy, 3 non-occlusive retinal vasculitis) following injection of pegcetacoplan into the eye. The events were observed after the first dose, occurring between 8 and 23 days (mean 12 days; median 10.5 days) after injection, with no specific lots implicated. Eight eyes had more than a 3-line decrease in visual acuity and 6 eyes had more than a 6-line decrease (the latter includes 2 eyes that were enucleated after they became blind and painful). Corticosteroids (oral, intravitreal, sub-Tenon, or combination) were used to treat retinal vasculitis in 12 out of 14 eyes. The etiology and outcomes of these events are still evolving. Intraocular inflammation was a factor in all these cases and is thought to be associated with the etiology of retinal vasculitis. There were no cases of occlusive retinal vasculitis reported in DERBY and OAKS.

Although not discussed in the American Society of Retina Specialists publication, an October 5, 2023 news release by Apellis, mentions that among 10 cases reported at that time, 6 recovered their vision fully or partially, 3 have severe vision impairment which is thought unlikely to be resolved, and 1 has the outcome pending. There are additionally 2 suspected events (unconfirmed) of retinal vasculitis with visual outcomes pending. [Apellis Announces Preliminary U.S. Net Revenues of Approximately \\$74 Million for SYFOVRE® \(pegcetacoplan injection\) in the Third Quarter of 2023 - Apellis Pharmaceuticals, Inc.](#)

The company, as part of their investigation into real-world safety events, identified internal structural variations in the 19-gauge x 1½ filter needle in certain injection kits that is used to withdraw the drug from the vial. Although a causal relationship has not been established between these 19-gauge filter needles and the events of retinal vasculitis, the company recommends that practitioners immediately discontinue use of injection kits that contain the 19-gauge filter and to use the kits with 18-gauge needle. Injection kits previously contained one of

Pegcetacoplan Monograph

two types of filter needles (either 18- or 19-gauge). The company is now only distributing injection kits with the 18-gauge filter needle. In the American Society of Retina Specialists report, needle type was known in 4 of the cases (2 used 19-gauge and 2 used 18-gauge).

- **Other warnings/precautions:**

- Endophthalmitis and Retinal Detachments
- Neovascular AMD. In clinical trials, use of pegcetacoplan was associated with increased rates of neovascular (wet) AMD or CNV (12% monthly, 7% QOM, and 3% sham) over 24 months. Patients receiving pegcetacoplan should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from pegcetacoplan administration.
- Intraocular inflammation
- Increased Intraocular Pressure

- **Adverse reactions**

- The most common adverse reaction (incidence $\geq 5\%$) are ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage

Table 2: Adverse Reactions in Study Eye in $\geq 2\%$ of Patients (Pooled OAKS and DERBY) Through Month 24

	PEG monthly (n=419)	PEG every other month (n=420)	Sham pooled (n=417)
Ocular discomfort (%)	13	10	11
Neovascular AMD (%)*	12	7	3
Vitreous floaters (%)	10	7	1
Conjunctival hemorrhage (%)	8	8	4
Vitreous detachment (%)	4	6	3
Retinal hemorrhage (%)	4	5	3
Punctate keratitis (%)	5	3	<1
Posterior capsule opacification (%)	4	4	3
Intraocular inflammation (%)^	4	2	<1
Increased intraocular pressure (%)	2	3	<1

Data from product package insert

*neovascular AMD included: exudative age-related macular degeneration, choroidal neovascularization

^Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

- **Exudative AMD (includes the preferred terms CNV and neovascular AMD):**

Patients with a history of or active CNV in the fellow eye were not excluded from the clinical trials. In the phase 2 FILLY trial, 37.8% of patients had CNV in the fellow eye. In OAKS and DERBY, fellow-eye CNV was identified at baseline in 20% of patients.

In the FILLY trial, the incidence of exudative AMD in the study eye in the overall population at 12 months was 20.9%, 8.9%, and 1.2% for PEG monthly, PEG EOM, and sham respectively. The risk of developing exudative AMD in the study eye was greater in those with a history of CNV in the fellow eye than in those without a history of CNV in the fellow eye (Table 3).

In OAKS and DERBY, the rate of investigator-diagnosed exudative AMD in the study eye in the overall population at 24 months was 12%, 7%, and 3% respectively. The risk of developing exudative AMD in the

Pegcetacoplan Monograph

study eye was greater in those with CNV in the fellow eye than in those without CNV in the fellow eye (Table 3).

Exudative AMD was reported more frequently in FILLY than in OAKS and DERBY. This difference may be explained by the greater number of patients with baseline CNV in the fellow eye in FILLY and that verification of diagnosis by a reading center was not required.

Development of exudative AMD in fellow-eye at 24 months in those who did not have CNV in that eye at baseline was 4.2% (14/335) 4.1% (14/339) 4.5% (15/330) for PEG monthly, PEG every other month, and pooled sham groups respectively.

In OAKS and DERBY, 86% of cases confirmed by reading center were classified occult CNV on fluorescein angiography. Nearly all patients who developed exudative AMD continued treatment with pegcetacoplan and were treated with anti-VEGF therapy. Treatment with anti-VEGF was at the discretion of the investigator. If anti-VEGF therapy is required, it should be administered separately from pegcetacoplan administration. None of the exudative AMD events were reported as serious adverse events.

Table 3: Development of Exudative AMD in Study Eye

	FILLY (12 months)			OAKS and DERBY (0-12 months)			OAKS and DERBY (0-24 months)		
	PEG monthly	PEG EOM	Sham	PEG monthly	PEG EOM	Sham	PEG monthly	PEG EOM	Sham
Overall population	18/86 (20.9%)	7/79 (8.9%)	1/81 (1.2%)	25/419 (6%)	17/419 (4.1%)	10/417 (2.4%)	51/419 (12.2%)	28/419 (6.7%)	13/417 (3.1%)
Active or history of CNV in fellow eye	12/36 (33.3%)	5/28 (17.9%)	0/29 (0.0%)	6/84* (7.1%)	4/81* (4.9%)	7/87* (8%)	14/84* (16.7%)	9/81* (11.1%)	8/87* (9.7%)
No active or history of CNV in fellow eye	6/50 (12%)	2/51 (3.9)	1/52 (1.9%)	19/335 (5.7%)	13/338 (3.8%)	3/331 (0.9%)	37/335 (11%)	19/338 (5.6%)	5/330 (1.5%)

*numbers were calculated using information posted on Apellis website Investors and Media/Events and Presentations [b78972dc-593c-4a62-a504-342d0d53de0f \(apellis.com\)](https://www.apellis.com/press-releases/2020-05-14)

- **Other Adverse Events of Interest**
 - Optic ischemic neuropathy at 24 months: 3 patients, 1 patient, and none in PEG monthly, PEG EOM, and sham respectively
 - Infectious endophthalmitis at 24 months: In OAKS 2 patients with 2 events in each active treatment group, none in sham group. In DERBY, there were no reports in any of the treatment groups
 - **Immunogenicity:** In OAKS and DERBY, the incidence of anti-pegcetacoplan peptide antibodies was pegcetacoplan was 4%) and 2.5% in patients treated with PEG monthly and PEG EOV respectively. . Because of the low incidence of anti-pegcetacoplan peptide antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of pegcetacoplan is unknown.
 - **Serious Treatment-Emergent Adverse Events in Study Eye (n (%)) number of events)**
 - **OAKS** 5 (2.3%) 7 (PEG monthly); 4 (1.9%) 4 (PEG EOM); 1 (0.5%) 1 (sham): 1 event each in pegcetacoplan monthly and EOM and none with sham were thought to be treatment-related
 - **DERBY** 4 (1.9%) 4 (PEG monthly); 2 (1.0%) 4 (PEG EOM); 2 (1.0%) 2 (sham): 3 events in pegcetacoplan monthly, 4 events with pegcetacoplan EOM and none with sham were thought to be treatment-related
- Deaths:** 6.4% (PEG monthly), 3.5% (EOM), 3.6% (sham)

Pegcetacoplan Monograph

Discontinuations due to an Adverse Event: 4.8% (PEG monthly), 3.3% (EOM), 3.6% (sham)

Other Considerations

- It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. Advise female patients of reproductive potential to use effective contraception during treatment with pegcetacoplan and for 40 days after the last dose. For women planning to become pregnant, the use of pegcetacoplan may be considered following an assessment of the risks and benefits.

Other Therapeutic Options

- Avacincaptad pegol was recently approved for treatment of GA due to AMD
- Several potential treatments, targeting various pathways, are under investigation. Examples include: anti-inflammatory and complement inhibition, antioxidative, reduction of toxic byproducts, visual cycle modulators, neuroprotection, cell-based therapies, mitochondrial enhancers.

Table 4: Comparison of Treatments for GA

	Efficacy	Safety
Pegcetacoplan	<ul style="list-style-type: none"> Slows progression of GA Difference vs sham in GA rate of growth at month 12* <ul style="list-style-type: none"> OAKS 21% (monthly); 16% (EOM) DERBY 12% (monthly); 11% (EOM) <p>No statistically significant differences across study arms on key secondary endpoints at 24 months (e.g., BCVA, maximum reading speed, Functional Reading Independence Index, low luminance visual acuity)</p>	<ul style="list-style-type: none"> Associated with increased risk of nAMD or CNV (12%, 7%, 3%) at 24 months Patients with a history of or active CNV in the study eye were excluded from the clinical trials. Patients with a history of CNV in the contralateral eye were included in the clinical trials. The risk of developing nAMD or CNV in the study eye was greater in those with a history of CNV in the contralateral eye in those treated with pegcetacoplan. Post-marketing: reports of at least 10 cases of occlusive retinal vasculitis following injection of pegcetacoplan into the eye.
Avacincaptad	<ul style="list-style-type: none"> Slows progression of GA Difference vs sham in GA rate of growth at month 12* <ul style="list-style-type: none"> GATHER 1: 35% GATHER 2: 17.7% <p>No impact on change in BCVA or low luminance BCVA at 12 months</p>	<ul style="list-style-type: none"> Associated with increased risk of nAMD or CNV (7% vs. 3%) at 12 months; at 24 months (unpublished) the risk was 12% vs. 9% Patients with active or history of macular neovascularization in either eye were excluded from the trials

*Based on non-transformed GA growth slope analysis (mm²)

Abbreviations: BCVA=best-corrected visual acuity; CNV=choroidal neovascularization; GA=geographic atrophy; nAMD=neovascular age-related macular degeneration

Projected Place in Therapy

Pegcetacoplan was the first FDA approved drug for the treatment of GA. Pegcetacoplan slowed the progression of GA over 24 months with the greatest effect occurring over the last 6 months. There was no reduction in the loss of visual acuity. Pegcetacoplan was associated with an increased risk of conversion to exudative AMD (12%, 7%, 3% for pegcetacoplan monthly, pegcetacoplan EOM, and sham respectively).

Pegcetacoplan Monograph

Patients with a history of or active CNV in the study eye were excluded from the clinical trials. Patients with a history of CNV in the fellow were included in the clinical trials. The risk of developing exudative AMD in the study eye was greater in those with a history of CNV in the fellow eye in those treated with pegcetacoplan.

In the absence of contraindications, use of pegcetacoplan should be restricted to the treatment of GA secondary to AMD.

References

Liao DS, Grossi FV, El Mehdi D, Gerber MR, et al. [Complement C3 Inhibitor Pegcetacoplan for Geographic Atrophy Secondary to Age-Related Macular Degeneration: A Randomized Phase 2 Trial](#). *Ophthalmology*. 2020 Feb;127(2):186-195.

Fleckenstein M, Mitchell P, Freund KB, Sadda S, et al. [The Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration](#). *Ophthalmology*. 2018 Mar;125(3):369-390.

SYFOVRE (pegcetacoplan injection) for intravitreal use [prescribing information online]. Waltham, MA. Apellis Pharmaceuticals, Inc. February 2023. Available at: [label \(fda.gov\)](#)

Heier JS, Lad EM, Holz FG, Rosenfeld PJ, et al.; OAKS and DERBY study investigators. [Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration \(OAKS and DERBY\): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials](#). *Lancet*. 2023 Oct 21;402(10411):1434-1448. doi: 10.1016/S0140-6736(23)01520-9

Efficacy of intravitreal pegcetacoplan in geographic atrophy: 24-month results from the phase 3 OAKS and DERBY trials <https://investors.apellis.com/static-files/78d1b209-7324-4c4c-8b20-bf7778493bae>

Safety of intravitreal pegcetacoplan in geographic atrophy: 24-month results from the OAKS and DERBY phase 3 trials <https://investors.apellis.com/static-files/faa3ab29-face-436a-b19d-4ec393f6436e>

24-Month Safety Results From the OAKS and DERBY Trials With Further Characterization of Exudative Age-Related Macular Degeneration [b78972dc-593c-4a62-a504-342d0d53de0f \(apellis.com\)](#)

Witkin AJ, Jaffe GJ, Srivastava SK, Davis JL, Kim JE. Retinal Vasculitis After Intravitreal Pegcetacoplan: Report From the ASRS Research and Safety in Therapeutics (ReST) Committee. *Journal of VitreoRetinal Diseases*. 2023;0(0). doi:[10.1177/24741264231220224](#)

Colijn J, Liefers B, Joachim N, et al; for the EyeNED Reading Center and EYE-RISK Consortium. [Enlargement of geographic atrophy from first diagnosis to end of life](#). *JAMA Ophthalmol*. Published online May 20, 2021. doi:10.1001/jamaophthalmol.2021.1407

Contact person: Deb Khachikian, PharmD, National PBM Clinical Pharmacy Program Manager, Formulary management, VA Pharmacy Benefits Management Services (10P4P)
