Intravitreal Complement Inhibitors (Syfovre & Izervay)

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Instructions for Use

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Related Policies

- n/a

Coverage Rationale

Geographic Atrophy (GA)

For initial coverage of **Syfovre (pegcetacoplan) or Izervay (avacincaptad pegol)** for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD), the following will be required:

- Diagnosis of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) as confirmed by one of the following:
  - Fundus photography (e.g. fundus autofluorescence [FAF])
  - Optical coherence tomography (OCT)
  - Fluorescein angiography **and**
- Prescribed by or in consultation with an ophthalmologist experienced in the treatment of retinal diseases

For reauthorization coverage of Izervay (avacincaptad pegol), the following will be required:

- Patient demonstrates positive clinical response to therapy (e.g., reduction in growth rate of GA lesion)

For reauthorization coverage of Syfovre (pegcetacoplan), the following will be required:

- Patient demonstrates positive clinical response to therapy (e.g., reduction in growth rate of GA lesion)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-

covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J2781	Injection, pegcetacoplan, intravitreal, 1 mg
J2782	Injection, avacincaptad pegol, 0.1 mg

ICD-10 Code	Description
H35.3113	Nonexudative age-related macular degeneration, right eye, advanced atrophic without subfoveal involvement
H35.3114	Nonexudative age-related macular degeneration, right eye, advanced atrophic with subfoveal involvement
H35.3123	Nonexudative age-related macular degeneration, left eye, advanced atrophic without subfoveal involvement
H35.3124	Nonexudative age-related macular degeneration, left eye, advanced atrophic with subfoveal involvement
H35.3133	Nonexudative age-related macular degeneration, bilateral, advanced atrophic without subfoveal involvement
H35.3134	Nonexudative age-related macular degeneration, bilateral, advanced atrophic with subfoveal involvement

Background

Age-related macular degeneration (AMD) is a progressive, degenerative disease of the central portion of the retina (the macula) that occurs with increasing frequency with age (American Academy of Ophthalmology [AAO] 2024). AMD is a leading cause of irreversible vision loss globally in patients > 50 years of age (Richard et al 2021). The National Eye Institute (NEI) estimated that AMD prevalence in the United States (U.S.) in 2010 was 2.1%, or 2.07 million people. By 2050, the estimated number of people with AMD is expected to more than double to 5.44 million (NEI Web site).

AMD is classified based on severity into 3 stages: early, intermediate, or advanced disease. Advanced disease is further classified into geographic atrophy (GA) or nAMD (AAO 2024, Richard et al 2021). Although GA and nAMD have distinct disease processes, they can occur simultaneously in the same eye (Syfovre dossier 2023). In its early stages, dry AMD is characterized by the presence of drusen, extracellular yellow deposits composed of lipid and protein aggregates at the posterior pole of the retina, and in the advanced stages as GA, a chronic progressive degeneration of the macula (Boyer et al 2017). GA is characterized by localized sharply demarcated atrophy of outer retinal tissue, RPE, and choriocapillaris. It typically starts in the perifoveal region and lesion enlargement expands over time to involve the fovea, leading to central scotomas and permanent loss of visual acuity (VA). GA is bilateral in most cases. Patients with GA experience variable visual field abnormalities. Perifoveal atrophy affects visual performance, including reading, driving, and low-light vision, whereas foveal involvement may profoundly affect central VA (Fleckenstein et al 2018, Shah et al 2025). In the U.S., GA affects nearly 1 million people and accounts for approximately one-quarter of cases of legal blindness (Liao et al 2020).
Multiple pathways of pathogenesis in GA have been suggested, however, the exact mechanism is not yet fully understood. Complement activation, lipid metabolism, retinal oxidative stress, drusen buildup, visual cycle toxic byproducts, and extracellular matrix modulation have been associated with the development of GA (Holz et al 2017, Richard et al 2021, Shah et al 2025).

Clinical Evidence

Izervay (avacincaptad pegol)

The efficacy and safety of avacincaptad pegol were evaluated in an 18-month, Phase 2/3, double-blind (DB), multi-center (MC), sham-controlled randomized controlled trial (RCT) (GATHER1, N = 286) (Jaffe et al 2021) and a 24-month, Phase 3, DB, MC, sham-controlled RCT (GATHER2, N = 448) (Izervay FDA clinical review 2023, Izervay dossier 2023, Khanani et al 2023) in patients with GA with nonfoveal lesions secondary to AMD. The primary endpoint in both trials was the mean rate of change in GA area over 12 months measured by fundus autofluorescence (FAF) at baseline, month 6, and month 12, assessed using square root transformation of the GA lesion area. Key secondary endpoints were mean change in best corrected visual acuity (BCVA) and low luminance (LL)-BCVA assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) charts from baseline to month 12.

- GATHER1 was conducted in 2 phases. Part 1 randomized patients to avacincaptad pegol 1 mg (n = 26) or 2 mg (n = 25) or sham (n = 26) injection. Subsequently in Part 2, patients were randomized to avacincaptad pegol 2 mg (n = 42), avacincaptad pegol 4 mg (n = 83), or sham (n = 84). Because of the drug viscosity, the 4 mg dose was administered as 2 separate 2 mg IVT injections. In Part 2, patients in the avacincaptad pegol 2 mg arm also received an additional sham administration (to mimic 2 injections), and patients who were in the sham arm received 2 sham administrations. Patients received IVT monthly injections for 18 months.
    - Treatment with both avacincaptad pegol 2 mg and 4 mg met the primary endpoint and reduced the mean GA lesion growth rate over 12 months: 27.4% (0.110 mm difference, p = 0.0072) for the avacincaptad pegol 2 mg group and 27.8% (0.124 mm difference, p = 0.0051) for the avacincaptad pegol 4 mg group compared with each corresponding sham-control group.
- GATHER2 randomized patients to avacincaptad pegol 2 mg IVT once monthly from day 1 to month 11 followed by monthly or every other month (EOM) injections from month 12 to 23 (n = 225) or sham once monthly until month 23 (n = 223). At month 12, randomization was repeated for patients receiving avacincaptad pegol 2 mg, with these patients randomly assigned to either continue receiving monthly avacincaptad pegol 2 mg or to receive avacincaptad pegol 2 mg EOM through month 23. All patients receiving sham on day 1 continued receiving sham throughout the study.
    - From baseline to month 12, the mean rate of square-root-transformed GA area growth (slope) was 0.336 mm/year (standard error [SE] 0.032) with avacincaptad pegol vs 0.392 mm/year (0.033) with sham, with an absolute difference of 0.056 mm/year (95% confidence interval [CI], 0.016 to 0.096; p = 0.0064), representing a 14% difference in GA area growth between the avacincaptad pegol group and the sham group. Month 24 results are not yet available.
- Differences in BCVA and LL-BCVA between the avacincaptad pegol group and the sham group were not statistically significant from baseline to month 12 in either trial.
- Patients in GATHER2 who developed new onset choroidal neovascularization (CNV) were eligible to remain in the study and receive concomitant anti-VEGF treatment. GA growth outcomes in patients who developed CNV during the trial and were treated with an anti-VEGF treatment were similar to the overall study population (difference in growth slope between avacincaptad and sham in overall population: 0.376 vs 0.400 mm^2 in CNV conversion patients).
- An 18-month open-label extension (OLE) study to assess long-term safety (N ~400) of avacincaptad pegol administered monthly in patients who completed GATHER2 through the 24-month visit has been completed, but the results have not yet been published (Clinicaltrials.gov Web site, Izervay FDA clinical review 2023).

Syfovre (pegcetacoplan)

The efficacy and safety of pegcetacoplan were evaluated in 2 unpublished, parallel, 24-month, Phase 3, DB, MC, sham-controlled, RCTs, OAKS (N = 637) and DERBY (N = 621), comparing the efficacy and safety of IVT pegcetacoplan administered every month (PM) or every other month (PEOM) with sham every month or EOM in patients with GA with or without subfoveal involvement (Syfovre dossier 2023; Syfovre Eye Care Professionals [ECP] Web site; Syfovre prescribing information 2024). The primary endpoint in both studies was the change from baseline to 12 months in total area (mm^2) of GA lesions as measured by FAF. The key secondary endpoint was mean change in BCVA assessed by the ETDRS charts.

- Pegcetacoplan met the primary endpoint in the OAKS study, demonstrating a statistically significant reduction in GA lesion growth at 12 months for both the PM (21%; p = 0.0004) and PEOM (16%; p = 0.0055) treatment arms vs the pooled sham arm. Pegcetacoplan demonstrated a trend toward reduced GA lesion growth at 12 months in the DERBY study for both the PM (12%; p = 0.0609) and PEOM (11%; p = 0.0853) treatment arms, but it did not reach statistical significance vs the pooled sham arm.
    - In prespecified combined analyses of the primary endpoint, pegcetacoplan reduced lesion growth by 16% (p < 0.0001 [nominal] vs sham) in the PM group and by 14% (p = 0.0014 [nominal] vs sham) in the PEOM group.
- In both studies, pegcetacoplan continued to demonstrate significant reductions in GA lesion growth in both the PM and PEOM treatment arms at 24 months, with increased treatment effects seen between months 18 to 24. In the OAKS trial, compared with sham injection, pegcetacoplan reduced GA lesion growth by 22% (p < 0.0001 [nominal]) in the PM group and by 18% (p = 0.0002 [nominal]) in the PEOM group. In the DERBY trial, pegcetacoplan reduced lesion growth by 18% (p = 0.0004 [nominal]) and by 17% (p = 0.003 [nominal]) in the PM and PEOM treatment arms, respectively.
    - In the combined analysis, pegcetacoplan decreased GA lesion growth by 21% and 17% in the PM and PEOM treatment arms, respectively. Over months 18 to 24, pegcetacoplan's treatment effect increased to 30% in the PM group and 24% in the PEOM group compared with sham.
- No statistically significant differences between study arms were detected in the prespecified secondary endpoints of visual function at 24 months, including BCVA, maximum reading speed, Functional Reading Independence (FRI) Index score, and microperimetry (mean threshold sensitivity [OAKS only]).
- In subgroup analyses, pegcetacoplan showed reductions in GA lesion growth in patients with nonsubfoveal (PM, 26%; p < 0.0001 and PEOM, 22%; p < 0.0001) and subfoveal lesions (PM, 19%; p < 0.0001 and PEOM, 16%; p = 0.0003) over 24 months in the OAKS and DERBY studies combined; p-values are nominal.
- A long-term OLE trial (GALE, N = 792) of patients who participated in OAKS, DERBY, or a previous Phase 1b was conducted (Wykoff et al 2025). The primary endpoint is incidence and severity of ocular and systemic adverse effects (AEs) up to 36 months. Patients received IVT pegcetacoplan on the same schedule received in their previous study, either monthly or EOM for up to 36 months. Those who received pegcetacoplan in OAKS and DERBY continued to receive pegcetacoplan at the same frequency in GALE, while those who received sham in OAKS and DERBY transitioned to receiving pegcetacoplan in GALE at the same frequency as they had previously received sham injections.
    - Pegcetacoplan was administered monthly (PM) or every other month (PEOM) to all study eyes in GALE. Eyes receiving pegcetacoplan in OAKS and DERBY continued the same regimen (PM-PM and PEOM-PEOM), while eyes observed with sham in OAKS and DERBY crossed over to receive pegcetacoplan at the same dosing interval in GALE (SM-PM and SEOM-PEOM). Safety and efficacy through the first 12 months of GALE were assessed, reflecting up to 36 months of continuous pegcetacoplan treatment. The main outcome measured was mean rate of change in GA area, total number of microperimetry scotomatous points, and adverse events.
    - Through the first 12 months of GALE, 92.0% (727/790) patient retention was observed. Across all eyes, including eyes with nonsubfoveal and subfoveal GA, pegcetacoplan reduced the mean rate of change in GA area up to 32% versus projected sham. Year after year, the reductions in the mean rate of change in GA area increased, with up to a 42% reduction observed in eyes with nonsubfoveal GA in the PM-PM group compared with projected sham in the first year of GALE. An 18% reduction in new scotomatous points (P = .0156) was observed with PM-PM at 36 months, highlighting a significant impact in a prespecified microperimetry analysis. Adverse events included 33 (4.5%) eyes with exudative AMD, 15 (1.9%) intraocular inflammation (classified as mild or moderate in severity), 1 (0.1%) ischemic optic neuropathy, and 1 (0.1%) infectious endophthalmitis. No events of vasculitis were reported.

Clinical Guidelines

The 2024 American Academy of Ophthalmology Age-Related Macular Degeneration Preferred Practice Pattern (AAO 2024) has not been updated to inform a place in therapy for Izervay or Syfovre. They note that the use of anti-VEGF agents may reduce blindness from neovascular AMD and could theoretically reduce the rate of legal blindness by up to

70% over 2 years. They also note that the use of antioxidant vitamins (i.e., vitamin C, vitamin E), lutein, zeaxanthin, and zinc in patients with intermediate AMD have been shown to reduce the progression toward more advanced stages of AMD by approximately 25% at 5 years.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

IZERVAY (avacincaptad pegol) is a complement inhibitor indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

SYFOVRE (pegcetacoplan) is a complement inhibitor indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

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Policy History/Revision Information

Date	Summary of Changes
7/17/2024	Approved by OptumRx P&T Committee
4/16/2025	Annual review. Updated references. Updated the coverage criteria as follows: Removed the following requirement of "Patient has not exceeded a total of 12 months treatment per eye" only for the reauthorization coverage of Izervay (avacincaptad pegol)
6/17/2026	Annual review. Updated background section and references.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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Southampton, PA 18966-9998
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You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

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200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
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Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

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Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다.1-800-332-6501 (TTY: 711)번으로 전화해 주십시오.

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Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

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Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-332-6501 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).

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