Intravitreal Complement Inhibitors (Syfovre & Izervay)

Policy Number: MC/PC 023
Effective Date: May 1, 2025

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* 2024). 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 e
understood. Complement activation, lipid metabolism, retinal oxidative stress,
byproducts, and extracellular matrix modulation have been associated with the development of GA (Holz et al 2017,
Richard *et al* 2021, Shah *et al* 2024).

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 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 is ongoing (*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 cl total area (mm^2) of GA lesions as measured by FAF. The key secondary endpoint wa he 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 trial is ongoing (*Apellis Medical Information response letter 2023*). 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. An interim analysis showed reductions in GA lesion growth in both the PM (24%; p < 0.0001) and PEOM (21%; p < 0.0001) treatment arms through 30 months vs pooled sham or projected sham in the GALE study, with increased treatment effect over time, reaching 39% (PM) and 32% (PEOM) between months 24 to 30. GA lesion growth in the sham crossover group (GALE, months 24 to 30) demonstrated a 15% reduction compared with previous sham average 6-month change (OAKS and DERBY, months 0 to 24). Results from months 0 to 6 for the sham crossover group are similar to the reduction in GA lesion growth observed in the first 6 months of OAKS and DERBY. Pegcetacoplan showed reductions in GA lesion growth in patients with nonsubfoveal lesions (PM: 31%; p < 0.0001 and PEOM: 26%; p < 0.0001) through 30 months vs pooled sham or projected sham, with increasing treatment effect over time, reaching 45% (PM) and 32% (PEOM) between months 24 to 30. Rates of investigator-determined new-onset nAMD in the study eye with 30 months of continuous treatment were 16.6% and 8.6% in the PM and PEOM arms, respectively, compared to 12.2% and 6.7% in the PM and PEOM arms, respectively, in OAKS and DERBY at month 24. No infectious endophthalmitis cases were observed during the first 6 months of GALE. The rate of intraocular inflammation (IOI) in pegcetacoplan-treated patients in OAKS, DERBY, and GALE was 0.26% per injection. This rate includes 4 cases reported in 2018 that were attributed to drug impurity, one of which was an event of non-infectious (culture-negative) endophthalmitis. There were no reports of occlusive or non-occlusive vasculitis or retinitis. During the first 6 months of GALE, 1 AE of ischemic optic neuropathy (ION) was reported in the PM arm.

Clinical Guidelines

The 2024 American Academy of Ophthalmology Age-Related Macular Degeneration Preferred Practice Pattern (AAO 2024) have 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 re) to 70% over 2 years. They also note that the use of antioxidant vitamins (i.e., vita 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).

References

1. American Academy of Ophthalmology. Age-related macular degeneration preferred practice pattern. 2024. https://www.aao.org/education/preferred-practice-pattern/age-related-macular-degeneration-ppp. Accessed March 6,2025.
2. Apellis Medical Information response letter. Pegcetacoplan GA – 30 month results of the Phase 3, open-label, extension (GALE) Study. September 2023.
3. Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. *Retina*. 2017;37(5):819-835.
4. ClinicalTrials.gov Web site. www.clinicaltrials.gov. Accessed May 27, 2024.
5. Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125(3):369-390.
6. Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeran Campagne M. Geographic atrophy. Clinical features and potential therapeutic approaches. *Ophthalmology*. 2014;121(5):1079-1091.
7. IZERVAY (avacincaptad pegol intravitreal solution) [package insert]. Northbrook, IL: Astellas Pharma US, Inc; February 2025.
8. Izervay [dossier], Parsippany, NJ: IVERIC bio; October 2023.
9. Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration. A randomized pivotal phase 2/3 trial. *Ophthalmology*. 2021;128(4):576-586.
10. Khanani AM, Patel SS, Staurenghi G, et al. Efficacy and safety of avacincaptad pegol in patients with geographic atrophy (GATHER2): 12-month results from a randomised, double-masked, phase 3 trial, *Lancet*. 2023;S0140-6736(23)01583-0. doi: 10.1016/S0140-6736(23)01583-0.
11. National Eye Institute. https://www.nei.nih.gov/. Accessed March 6,2025.
12. Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration. *Ophthalmology.* 2020;127(2):186-195.
13. Richard AJ, Duker JS, Reichel E. Geographic atrophy: where we are now and where we are going. *Curr Opin Ophthalmol.* 2021;32(3):247-252.
14. Shah YS, Nielsen MK, Do DV, Bhagat N, Lim JI. Geographic atrophy. Reviewed September 22 2024. https://eyewiki.aao.org/Geographic_Atrophy#Disease. Accessed March 6, 2025.

15. Syfovre [dossier], Waltham, PA: Apellis Pharmaceuticals, Inc.; March 15, 2(
16. Syfovre Web site. U.S. Eye Care Professionals. https://syfovreecp.com/. Ac
17. SYFOVRE (pegcetacoplan injection), for intravitreal use [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc;December 2024.

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)

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.

Archived Policy Versions (Internal Only)

Effective Date	Policy Number	Policy Title
mm/dd/yyyy – mm/dd/yyyy	######	Title of Policy Hyperlinked to KL or Other Internal Location

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

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*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

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)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

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.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer1-800-332-6501 (TTY: 711).

Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода.Звоните 1-800-332-6501 (телетайп: 711).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al1-800-332-6501 (TTY: 711).

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).

Traditional Chinese: 注意：如果您使用繁體中文， 您可以免費獲得語言援助服務。請 致電 1-800-332-6501 (TTY: 711)

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).