Policy Name	Clinical Policy –Complement Inhibitors for Geographic Atrophy
Policy Number	1349.00
Department	Clinical Product & Development
Subcategory	Medical Management
Original Approval Date	07/12/2023
Current MPC/CCO Approval Date	07/10/2024
Current Effective Date	11/01/2024

Company Entities Supported (Select All that Apply):
X Superior Vision Benefit Management
X Superior Vision Services
X Superior Vision of New Jersey, Inc.
X Block Vision of Texas, Inc. d/b/a Superior Vision of Texas
X Davis Vision
(Collectively referred to as 'Versant Health' or 'the Company')

ACRONYMS and DEFINITIONS	
ADA	Anti-drug antibodies
AMD	Age Related Macular Degeneration
APL-2	Organic chemical ID for pegcetacoplan
Biologic[al] [drug]	Biologics are large, living molecules, developed to disrupt or replace an adverse biological reaction within living organisms. Biologicals vary from chemical formulations in that they interact biologically instead of chemically to induce a therapeutic change.
CNV	Choroidal neovascularization; the exudative type of age related macular degeneration and includes abnormal growth of vessels from the choroidal vasculature to the neurosensory retina
DA	Disc Area
DD	Disc Diameter
FA	Fluorescein Angiogram

FAF	Fundus autofluorescence.
GA	Geographic atrophy
OCT	Optical Coherence Tomography

PURPOSE

To provide the medical necessity criteria to support the indication(s) for complement inhibitors. Applicable procedure codes are also defined.

POLICY

A. Background

Syfovre and Izervay are FDA approved treatments for geographic atrophy (GA), a complication of dry age-related macular degeneration (AMD). The mechanism of action for both drugs involves the complement system, a part of the immune system. They block specific complement proteins, aiming to reduce inflammation and damage to retinal cells which causes geographic atrophy. Syfovre has been associated with rare serious adverse events such as ischemic optic neuropathy and retinal vasculitis. For Izervay, the data currently shows that there is potentially lower risk of serious adverse events compared to Syfovre, however data on long-term safety profiles is still emerging. Individuals receiving either drug need to be monitored for signs of neovascular AMD.

B. Medically Necessary

1. Initial treatment with Syfovre may be considered medically necessary for adult patients when all the following criteria are met:

    a. Patient has diagnosis of vision threatening geographic atrophy (GA) secondary to age related macular degeneration.
    b. The GA is in the fovea, or, if extra foveal than total measure is greater than or equal (≥) to 0.5 DD or 0.25 DA.[1]

2. Initial treatment with Izervay may be considered medically necessary for adult patients when all the following criteria are met:

    a. Patient has diagnosis of vision threatening geographic atrophy (GA) secondary to age related macular degeneration.
    b. The GA is extra foveal;

[1] OAKS and DERBY trials

c. Total lesion area should be between 2.5 and 17.5 mm2 (1–7 disc areas). For multifocal lesions, at least 1 lesion should be 1.25 mm^2 (0.5 disc area) or larger.

3. Retreatment with Syfovre or Izervay may be medically necessary and approved when the submitted documentation shows:

   a. The above criteria are met, and
   b. The last treatment was at least 25 days prior; and,
   c. The intraocular pressure remains controlled; and,
   d. The previous treatment with the same drug was well tolerated; and,
   e. The patient has been evaluated for conversion to CNV.

C. Not Medically Necessary

The request for Syfovre or Izervay may not be medically necessary when:

1. Patient has ocular or periocular infections; or,
2. Patient has active intraocular inflammation; or,
3. The patient's GA is secondary to a condition other than AMD, such as toxic maculopathy, or Stargardt [2]; or,
4. The eye has no visual acuity to preserve or protect from the GA.

D. Documentation

Medical necessity must be supported by adequate and complete documentation in the patient's medical record that describes the procedure and the medical rationale for it as in requirements above. All items must be available upon request to initiate or sustain previous payments. For any retrospective review, a full operative report and the medical plan of care is needed.

Every page of the record must be legible and include appropriate patient identification information (e.g., complete name, date(s) of service). Services provided/ordered must be authenticated by the physician, in a handwritten or electronic signature. Stamped signatures are not acceptable. The required documentation to support medical necessity includes full clinical notes including the:

1. Anterior and posterior segment exams; and,
2. Measurements of the intraocular pressure and best corrected visual acuity; and,
3. Results of relevant testing including any OCT, FA, color fundus photographs, or FAF; and,
4. The evaluation and medical plan of care.

[2], [10] Appelis Syfovre Phase 3 trial exclusions Appelis Syfovre Phase 3 trial exclusions

E. Procedural Detail

CPT Codes	
J2781	Injection, pegcetacoplan, 1 mg (Syfovre)
J2782	Injection, avacincaptad pegol, 0.1 mg (Izervay)
67028	Intravitreal injection of a pharmacologic agent, separate procedure.
Required Modifiers	
L, R, or 50 (bilateral)	
JW or JZ	Drug amount discarded/not administered to any patient or Zero drug amount discarded/not administered to any patient
Invalid Modifiers	
24, 25, 26, 57, 95, TC	

DISCLAIMER and COPYRIGHTS

This clinical policy is provided for information purposes only and does not constitute medical advice. Versant Health, Inc., and its affiliates (the "Company") do not provide health care services and cannot guarantee any results or outcomes. Treating doctors are solely responsible for determining what services or treatments to provide to their patients. Patients (members) should always consult their doctor before making any decisions about medical care.

Subject to applicable law, compliance with this clinical policy is not a guarantee of coverage or payment. Coverage is based on the terms of an individual's particular benefit plan document, which may not cover the service(s) or procedure(s) addressed in this clinical policy. The terms of the individual's specific benefit plan are always determinative.

Every effort has been made to ensure that the information in this clinical policy is accurate and complete, however the Company does not guarantee that there are no errors in this policy or that the display of this file on a website is without error. The company and its employees are not liable for any errors, omissions, or other inaccuracies in the information, product, or processes disclosed herein. Neither the company nor the employees represent that the use of such information, products, or processes will not infringe on privately owned rights. In no event shall the Company be liable for direct, indirect, special, incidental, or consequential damages arising out of the use of such information, product, or process.

COMPANY'S COPYRIGHT STATEMENT Except for any copyrights described below, this clinical policy is confidential and proprietary, and no part of this clinical policy may be copied, distributed, or used without Versant Health, or its applicable affiliates express prior written approval.

AMA COPYRIGHT STATEMENT CPT© is the 2002-2024 copyright of the American Medical Association. All Rights Reserved. CPT™ is a registered trademark of the American Medical Association. Applicable FARS/DFARS apply to government use. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein.

RELATED POLICIES	
1317	Vascular Endothelial Growth Factor Inhibitors
1346	Corticosteroid Implants and Injections

DOCUMENT HISTORY		
Approval Date	***Revision***	***Effective Date***
07/12/2023	Initial policy	01/01/2024
07/10/2024	Change of policy name; addition of new drug (Izervay) with criteria.	11/01/2024

REFERENCES AND SOURCES

1. Bakri SJ, Bektas M, Sharp D, et.al. Geographic atrophy: Mechanism of disease, pathophysiology, and role of the complement system. J Manag Care Spec Pharm. 2023 May;29(5-a Suppl): S2-S11. doi: 10.18553/jmcp.2023.29.5-a. s2. PMID: 37125931; PMCID: PMC10408405.
2. Buch H, Nielsen NV, Vinding T, et.al. 14-year incidence, progression, and visual morbidity of age-related maculopathy: the Copenhagen City Eye Study. Ophthalmology. 2005 May;112(5):787-98. doi: 10.1016/j.ophtha.2004.11.040. PMID: 15878058.
3. Garg A, Nanji K, Tai F, et.al. The effect of complement C3 or C5 inhibition on geographic atrophy secondary to age-related macular degeneration: A living systematic review and meta-analysis. Surv Ophthalmol. 2023 Nov 24: S0039-6257(23)00160-1. doi: 10.1016/j.survophthal.2023.11.008. Epub ahead of print. PMID: 38008405.
4. 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 Apr;128(4):576-586. doi: 10.1016/j.ophtha.2020.08.027. Epub 2020 Sep 1. PMID: 32882310.
5. Kolev M, Barbour T, Baver S, et.al. With complements: C3 inhibition in the clinic. Immunol Rev. 2023 Jan;313(1):358-375. doi: 10.1111/imr.13138. Epub 2022 Sep 25. PMID: 36161656.

6. Liao DS, Grossi FV, El Mehdi D, 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. doi: 10.1016/j.ophtha.2019.07.011. Epub 2019 Jul 16. PMID: 31474439.
7. Liao DS, Grossi FV, Wykoff CC, et.al. Re: Minimizing risks to patients by improving presentation of clinical trial results in geographic atrophy trials (Ophthalmol Retina. 2022; 6:337-338). Ophthalmol Retina. 2022 Nov;6(11):1109. doi: 10.1016/j.oret.2022.08.010. PMID: 36334931.
8. Mai J, Riedl S, Reiter GS, et.al. Comparison of Fundus Autofluorescence Versus Optical Coherence Tomography-based Evaluation of the Therapeutic Response to Pegcetacoplan in Geographic Atrophy. Am J Ophthalmol. 2022 Dec; 244:175-182. doi: 10.1016/j.ajo.2022.06.023. Epub 2022 Jul 16. PMID: 35853489.
9. Nittala MG, Metlapally R, Ip M, et.al. Association of Pegcetacoplan with Progression of Incomplete Retinal Pigment Epithelium and Outer Retinal Atrophy in Age-Related Macular Degeneration: A Post Hoc Analysis of the FILLY Randomized Clinical Trial. JAMA Ophthalmol. 2022 Mar 1;140(3):243-249. doi: 10.1001/jamaophthalmol.2021.6067. PMID: 35113137; PMCID: PMC8814977.
10. Patel SS, Lally DR, Hsu J, et.al. Avacincaptad pegol for geographic atrophy secondary to age-related macular degeneration: 18-month findings from the GATHER1 trial. Eye (Lond). 2023 Dec;37(17):3551-3557. doi: 10.1038/s41433-023-02497-w. Epub 2023 Mar 24. Erratum in: Eye (Lond). 2023 May 26; PMID: 36964259; PMCID: PMC10686386.
11. Riedl S, Vogl WD, Mai J, et.al. The Effect of Pegcetacoplan Treatment on Photoreceptor Maintenance in Geographic Atrophy Monitored by Artificial Intelligence-Based OCT Analysis. Ophthalmol Retina. 2022 Nov;6(11):1009-1018. doi: 10.1016/j.oret.2022.05.030. Epub 2022 Jun 3. PMID: 35667569. Seddon JM, Rosner B. Validated Prediction Models for Macular Degeneration Progression and Predictors of Visual Acuity Loss Identify High-Risk Individuals. Am J Ophthalmol. 2019 Feb; 198:223-261. doi: 10.1016/j.ajo.2018.10.022. Epub 2018 Oct 31. PMID: 30389371; PMCID: PMC6469720.
12. Rofagha S. Minimizing Risks to Patients by Improving Presentation of Clinical Trial Results in Geographic Atrophy Trials. Ophthalmol Retina. 2022 May;6(5):337-338. doi: 10.1016/j.oret.2021.12.018. PMID: 35525573.
13. Shughoury A, Sevgi DD, Ciulla TA. The complement system: a novel therapeutic target for age-related macular degeneration. Expert Opin Pharmacother. 2023 Sep-Dec;24(17):1887-1899. doi: 10.1080/14656566.2023.2257604. Epub 2023 Sep 11. PMID: 37691588.
14. Tolentino MJ, Tolentino AJ. Investigational drugs in clinical trials for macular degeneration. Expert Opin Investig Drugs. 2022 Oct;31(10):1067-1085. doi: 10.1080/13543784.2022.2113375. Epub 2022 Sep 20. PMID: 35962560.
15. Vogl WD, Riedl S, Mai J, et.al. Predicting Topographic Disease Progression and Treatment Response of Pegcetacoplan in Geographic Atrophy Quantified by Deep Learning. Ophthalmol Retina. 2023 Jan;7(1):4-13. doi: 10.1016/j.oret.2022.08.003. Epub 2022 Aug 7. PMID: 35948209.
16. Wykoff CC, Rosenfeld PJ, Waheed NK, et.al. Characterizing New-Onset Exudation in the Randomized Phase 2 FILLY Trial of Complement Inhibitor Pegcetacoplan for Geographic Atrophy. Ophthalmology. 2021 Sep;128(9):1325-1336. doi: 10.1016/j.ophtha.2021.02.025. Epub 2021 Mar 10. PMID: 33711380.

SOURCES

1. AAO EyeNet Magazine. Feb 2023. “New Treatmens and New Biomarkers for Geographic Atrophy.” https://www.aao.org/eyenet/article/novel-therapies-new-biomarkers-geographic-atrophy. Accessed 6/2024.
2. Appelis SYFOVRE™ OAK and DERBY study results. https://syfovreecp.com/syfovre-clinical-trial-program/. Accessed 2/2024.
3. Boyer DS. Emerging treatments for advanced dry AMD. Modern Retina Digital Edition. Spring 2022; Vol. 2:1. https://www.modernretina.com/view/emerging-treatments-for-advanced-dry-amd. Accessed 2/2024.
4. Appelis announces 24 month results in phase 3 studies. https://investors.apellis.com/news-releases/news-release-details/apellis-announces-24-month-results-showing-increased-effects . Accessed 2/2024.
5. FDA NDA 217225, IZERVAY™ (avacincaptad pegol intravitreal solution) Initial U.S. Approval: 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217225s000lbl.pdf. Accessed 4/2024.
6. Iveric bio, Inc. Izervay Prescribing Information; https://ivericbio.com/wp-content/uploads/IZERVAY-avacincaptad-pegol-intravitreal-solution-PI_Final_8.4.23.pdf. Accessed 2/2024.
7. Kuriyan, Ajay E. Intravitreal pegcetacoplan may be linked with increased incidence of exudative AMD. Dec. 2021. https://www.aao.org/education/editors-choice/intravitreal-pegcetacoplan-may-be-linked-with-incr . Accessed 2/2024.
8. NIH NLM An extension study to evaluate the long-term safety and efficacy of pegcetacoplan (APL-2) in subjects with geographic atrophy secondary to AMD. 2022. Phase 3, open label invitation study for DERBY an OAKS participant. Derby, NCT03525613) or Study APL2-304 (Oaks, NCT03525600). https://beta.clinicaltrials.gov/study/NCT04770545?distance=50&term=DERBY%20OAKS&rank=1&tab=results No results posted. Accessed 2/2024.
9. NIH NLM A Study to Compare the Efficacy and Safety of Intravitreal APL-2 Therapy with Sham Injections in Patients with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (Derby). Active. No results posted. https://clinicaltrials.gov/ct2/show/NCT03525613?term=NCT03525613&draw=2&rank=1 . Accessed 3/14/2023.
10. NIH US National Library of Medicine. Phase 2 study of pegcetacoplan therapy in patients with geographic atrophy (FILLY). https://clinicaltrials.gov/ct2/show/results/NCT02503332?term=pegcetacoplan&cond=retinal+geographic+atrophy&draw=2&rank=1.
11. NIH NLM Apellis sponsored Safety assessment of APL-2 in patients with neovascular AMD. https://clinicaltrials.gov/ct2/show/results/NCT03465709?term=pegcetacoplan&cond=%22Macular+Degeneration%22&draw=2&rank=2 (no publications available). 2020. Accessed 3/14/2023.
12. NIH NLM Pegcetacoplan in Neovascular AMD. Terminated with results. https://beta.clinicaltrials.gov/study/NCT03465709?distance=50&cond=Age-Related%20Macular%20Degeneration&term=APL-2&rank=4&tab=results. Accessed 2/2024.
13. SYFOVRE™ Prescribing Information. https://pi.apellis.com/files/PI_SYFOVRE.pdf. Accessed 2/2024.