Policy Name	Clinical Policy – SYFOVFRE
Policy Number	1349.00
Department	Clinical Product & Strategy
Subcategory	Medical Management
Original Approval Date	07/12/2023
Current MPC/CCO Approval Date	07/12/2023
Current Effective Date	01/01/2024

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
IOI	Intraocular inflammation
Immunogenicity	The ability of therapeutic protein products (biologics) to stimulate an immune response, specifically, the development of antidrug antibodies (ADAs).
OCT	Optical Coherence Tomography
PM / PEOM	Monthly/every other month.
TEAE	Treatment emergent adverse event

PURPOSE

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

POLICY

A. Background

Syfovre is a C-3 complement inhibitor indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)[1]. Syfovre acts to control the mean growth rate of a GA lesion; it does not eradicate the lesion. Future indications for this novel treatment may include GA prevention.[1]

As one of new class of biological drugs, Syfovre has varying effects and risks from the typical chemical drug formulations. The complex molecular formulation of biologicals increases the risk for batch variations. These unpredictable variations may result in immune responses due to anti-drug antibodies (ADA). ADA events may occur in addition to the clinically observed adverse drug reactions which include neovascular AMD, endophthalmitis, and retinal detachment.[2]

B. Medically Necessary

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

[1] Jaffe C5 inhibitor, 2021
[2] Appelis, prescribing information, 2023.

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.[3]
c. Subfoveal involvement, secondary to the AMD, is not a treatment exclusion[4].

2. Retreatment with Syfovre 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 Syfovre treatment was well tolerated; and,
e. The patient has been evaluated for conversion to CNV.

C. Not Medically Necessary

A request for Syfovre may not be approved when:

1. Patient has ocular or periocular infections and/or active intraocular inflammation; or,
2. The patient's GA is secondary to a condition other than AMD, such as toxic maculopathy, or Stargardt [5]; or,
3. The eye has no visual acuity to preserve or protect from the encroaching GA.

D. Documentation

Required documentation 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.

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/or clinical care plan 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.

[3] OAKS and DERBY trials
[4] OAKS and DERBY trials
[5], [10] Appelis Syfovre Phase 3 trial exclusions Appelis Syfovre Phase 3 trial exclusions

E. Procedural Detail

CPT Codes	
C9151	Injection, pegcetacoplan, 1 mg
67028	Intravitreal injection of a pharmacologic agent, separate procedure.
Required Modifiers	
L, R, or Bilateral	
JZ	Zero drug amount discarded/not administered to any patient
Invalid Modifiers	
24, 25, 26, 57, 95, TC	

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COMPANY'S COPYRIGHT STATEMENT

AMA COPYRIGHT STATEMENT

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

REFERENCES AND SOURCES

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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. Appelis SYFOVRE™ OAK and DERBY study results. https://syfovreecp.com/syfovre-clinical-trial-program/. Accessed 5/15/2023.
2. 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 5/5/2023.
3. 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 3/14/2023.
4. 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
5. 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 3/14/2023.
6. 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.

7. 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.
8. 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.
9. NIH NLM Assessment of safety, tolerability, and pharmacokinetics of APL-2 with wet AMD (ASAP II). Interventional study with 1 time varying dose of APL-2 (4 mg, 10 mg, 20 mg.). Adverse effects measured indicates dose related increase in TEAR. https://beta.clinicaltrials.gov/study/NCT02461771?distance=50&cond=Age-Related%20Macular%20Degeneration&term=APL-2&rank=6&tab=results. (No publications available). Accessed 3/14/2023.
10. 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 3/14/2023.
11. SYFOVRE™ Prescribing Information. https://pi.apellis.com/files/PI_SYFOVRE.pdf. Accessed 5/15/2023.