Clinical Policy: Pegcetacoplan (Empaveli, Syfovre)

Reference Number: LA.PHAR.524
Effective Date: 05.10.24
Last Review Date: 08.20.25~~12.11.24~~ Coding Implications
Line of Business: Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

****Please note: This policy is for medical benefit****

Description
Pegcetacoplan (Empaveli®, Syfovre®) is a C3/C3b complement inhibitor.

FDA Approved Indication(s)
Empaveli is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

Syfovre is indicated for the treatment of adult patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Louisiana Healthcare Connections® that Empaveli and Syfovre are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Paroxysmal Nocturnal Hemoglobinuria (must meet all)**:**

1. Diagnosis of PNH;
2. Request is for Empaveli;
3. Prescribed by or in consultation with a hematologist;
4. Age ≥ 18 years;
5. Flow cytometry shows detectable glycosylphosphatidylinositol (GPI)-deficient hematopoietic clones or ≥ 10% PNH cells;
6. Documentation of hemoglobin < 10.5 g/dL;
7. Empaveli is not prescribed concurrently with either of the following (a and b):
   a. Syfovre;
   b. Another FDA-approved product for PNH (e.g., Soliris®, Ultomiris®, Fabhalta®, Voydeya™, Bkemv™~~),~~™, Epysqli®, PiaSky®), unless the member is in a 4-week period of cross-titration between Soliris/Bkemv/Epysqli and Empaveli;*
   **Provider must submit attestation of the presence or absence of concomitant Soliris/Bkemv/Epysqli therapy*

8. Dose does not exceed 2,160 mg per week or 1,080 mg every 3 days (total 10 doses per month) with documentation of a lactate dehydrogenase (LDH) level greater than 2 times the upper limit of normal (ULN).

Approval duration: 6 weeks *(if within cross-titration period with Soliris)*, or 6 months

B. Geographic Atrophy (must meet all)**:**

1. Diagnosis of GA secondary to AMD;
2. GA has all of the following characteristics confirmed on fundus autofluorescence imaging (a, b, c, and d):
   a. Total GA area ≥ 2.5 and ≤ 17.5 mm^2 (1 and 7 disk areas [DA] respectively);
   b. If GA is multifocal, at least one focal lesion ≥ 1.25 mm^2 (0.5 DA);
   c. GA lesion(s) are not contiguous with any areas of peripapillary atrophy;
   d. Presence of hyperautofluorescence in the junctional zone of GA;
3. Request is for Syfovre;
4. Prescribed by or in consultation with an ophthalmologist;
5. Age ≥ 60 years;
6. Best corrected visual acuity (BCVA) of 24 letters or better on Early Treatment Diabetic Retinopathy Study (ETDRS) charts (approximately 20/320 Snellen equivalent);
7. Member does not have either of the following (a and b):
   a. Diagnosis of any condition that may cause GA, including but not limited to pathologic myopia, Stargardt disease, cone rod dystrophy, and toxic maculopathies like Plaquenil maculopathy;
   b. History of or active choroidal neovascularization (CNV) in the eye(s) affected by GA;
8. Syfovre is not prescribed concurrently with Empaveli;
9. Dose does not exceed 15 mg (0.1 mL of 150 mg/mL solution) in each affected eye every 25 days.

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255;
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy ~~for the relevant line of business:~~ LA.PMN.53 ~~for Medicaid~~.

II. Continued Therapy

A. Paroxysmal Nocturnal Hemoglobinuria (must meet all)**:**

a. Currently receiving medication via Louisiana Healthcare Connections benefit or member has previously met initial approval criteria;
2. Request is for Empaveli;
3. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in <u>any</u> of the following parameters (a – f):

a. Improved measures of intravascular hemolysis or extravascular hemolysis (e.g., normalization of lactate dehydrogenase, reduced absolute reticulocyte count, reduced bilirubin);
b. Reduced need for red blood cell transfusions;
c. Increased or stabilization of hemoglobin levels;
d. Less fatigue;
e. Improved health-related quality of life;
f. Fewer thrombotic events;

4. Empaveli is not prescribed concurrently with either of the following (a and b):
   a. Syfovre;
   b. Another FDA-approved product for PNH (e.g., Soliris, Ultomiris, Fabhalta, Voydeya, Bkemv, Epysqli, PiaSky);
5. If request is for a dose increase, new dose does not exceed 2,160 mg per week or 1,080 mg every 3 days (total 10 doses per month) with documentation of an LDH level greater than 2 times the ULN.

Approval duration: ~~6~~12 months

B. Geographic Atrophy (must meet all)**:**
1. Currently receiving medication via Louisiana Healthcare Connections benefit or member has previously met initial approval criteria;
2. Request is for Syfovre;
3. Member is responding positively to therapy;
4. Syfovre is not prescribed concurrently with Empaveli;
5. If request is for a dose increase, new dose does not exceed 15 mg (0.1 mL of 150 mg/mL solution) in each affected eye every 25 days.

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one LA.PMN.255;
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy ~~for the relevant line of business:~~ LA.PMN.53 ~~for Medicaid~~.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy~~ies~~ LA.PMN.53 ~~for Medicaid, or evidence of coverage documents~~.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AMD: age-related macular degeneration
BCVA: best corrected visual acuity
CNV: choroidal neovascularization
DA: disk area
ETDRS: Early Treatment Diabetic Retinopathy Study

FDA: Food and Drug Administration
GA: geographic atrophy
GPI: glycosylphosphatidylinositol
LDH: lactate dehydrogenase
PNH: paroxysmal nocturnal hemoglobinuria
REMS: Risk Evaluation and Mitigation Strategy
ULN: upper limit of normal

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s):
  - Empaveli: hypersensitivity to pegcetacoplan or any of the excipients; for initiation in patients with unresolved serious infection caused by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B
  - Syfovre: ocular or periocular infections; active intraocular inflammation; hypersensitivity
- Boxed warning(s):
  - Empaveli: serious infections caused by encapsulated bacteria; Empaveli is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)
  - Syfovre: none reported

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Empaveli	PNH	1,080 mg SC twice weekly via a commercially available infusion pump or the Empaveli on body injector For patients switching from Soliris/Bkemv/Epysqli, initiate Empaveli while continuing Soliris/-Bkemv/Epysqli at its current dose. After 4 weeks, discontinue Soliris/Bkemv/Epysqli before continuing on monotherapy with Empaveli. For patients switching from Ultomiris, initiate Empaveli no more than 4 weeks after the last dose of Ultomiris. For LDH levels > 2x ULN, adjust the dosing regimen to 1,080 mg every three days.	1,080 mg/dose
Syfovre	GA	15 mg (0.1 mL of 150 mg/mL solution) via intravitreal injection to each affected eye once every 25 to 60 days	15 mg/25 days

VI. Product Availability

Drug Name	Availability
Empaveli	Single-dose vial for subcutaneous injection: 1,080 mg/20 mL
Syfovre	Single-dose vial for intravitreal injection: 150 mg/mL

VII. References

1. Empaveli Prescribing Information. Waltham, MA: Apellis Pharmaceuticals, Inc.; February 2024. Available at: https://empavelihcp.com/. Accessed ~~May 8, 2024~~April 16, 2025.
2. Wong R, Pullon H, Deschatelets P, et al. Inhibition of C3 with APL-2 results in normalization of markers of intravascular and extravascular hemolysis in subjects with paroxysmal nocturnal hemoglobinuria (PNH). Poster presented at: American Society of Hematology (ASH). 2018.
3. Hillmen P, Szer J, Weitz IC, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. NEJM March 2021;384:1028-37.
4. Bhak RY, Mody-Patel N, Baver SB, et al. Comparative effectiveness of pegcetacoplan versus ravulizumab in patients with paroxysmal nocturnal hemoglobinuria previously treated with eculizumab: a matching-adjusted indirect comparison. Abstract 2581. Presented at the 62nd American Society of Hematology Annual Meeting and Exposition, Dec 2-11, 2020.
5. Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood 2005; 106(12):3699-3709. Doi:10.1182/blood-2005-04-1717.
6. Apellis Pharmaceuticals, Inc. Study of pegcetacoplan (APL-2) therapy in patients with geographic atrophy (FILLY). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02503332. Accessed May ~~15, 2024~~1, 2025.
7. 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; 127(2): 186-195.
8. Apellis Pharmaceuticals, Inc. 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). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03525600. Accessed May ~~15, 2024~~1, 2025.
9. Apellis Pharmaceuticals, Inc. 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 (OAKS). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03525613. Accessed May ~~15, 2024~~1, 2025.
10. Goldberg R, Heier JS, Wyoff CC, et al. Abstract: Efficacy of intravitreal pegcetacoplan in patients with geographic atrophy (GA): 12-month results from the phase 3 OAKS and DERBY studies. Investigative Ophthalmology & Visual Science. 2022; 63(7): 1500.
11. Apellis Pharmaceuticals, Inc. Apellis announces pegcetacoplan showed continuous and clinically meaningful effects at month 18 in phase 3 DERBY and OAKS studies for geographic atrophy (GA). News release published March 16, 2022. Available at: https://investors.apellis.com/news-releases/news-release-details/apellis-announces-pegcetacoplan-showed-continuous-and-clinically. Accessed May ~~15, 2024~~1, 2025.
12. American Academy of Ophthalmology Retina/Vitreous Committee. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration. San Francisco, CA: American Academy of Ophthalmology; ~~2019.~~2024. Published February 2025. Available at:

https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp. Accessed May ~~15, 2024~~1, 2025.
13. Syfovre Prescribing Information. Waltham, MA: Apellis Pharmaceuticals, Inc.; ~~November 2023.~~December 2024. Available at: https://syfovre.com. Accessed ~~May 8, 2024.~~April 16, 2025.
14. Regillo CD, Nijm LM, Shechtman DL, et al. Considerations for the identification and management of geographic atrophy: Recommendations from an expert panel. Clinical Ophthalmology. 2024; 18: 325-335.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J2781	Injection, pegcetacoplan, intravitreal, 1 mg
J7799	Noc drugs, other than inhalation drugs, administered through dme

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Converted corporate to local policy.	04.04.24	05.10.24
For PNH, added Fabhalta, Voydeya, and Bkemv to the list of therapies that Empaveli should not be prescribed concurrently with; for GA, clarified that diagnostic characteristics must be confirmed on fundus autofluorescence imaging per health plan request and in alignment with pivotal study design; revised Empaveli contraindications in Appendix C per updated prescribing information; references reviewed and updated.	12.11.24	02.24.25
Annual review: for PNH, added Epysqli and PiaSky to the list of therapies that Empaveli should not be prescribed concurrently with, added improvement of extravascular hemolysis as an example of positive response to therapy, and revised continued approval duration from 6 to 12 months as PNH is a chronic condition; updated Syfovre contraindications in Appendix C to include hypersensitivity per updated prescribing information; references reviewed and updated	08.20.25	

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing

this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

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