Clinical Policy: Pegcetacoplan (Empaveli, APL-2)

Reference Number: ERX.SPA.427
Effective Date: 05.14.21
Last Review Date: 11.22
Line of Business: Commercial, Medicaid

Revision Log

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

Description
Pegcetacoplan (Empaveli™, APL-2™/®) is a C3/C3b complement inhibitor.

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

[Pending] APL-2 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Empaveli and APL-2 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. APL-2;
   b. Another FDA-approved product for PNH (e.g., Soliris®, Ultomiris®), unless the member is in a 4-week period of cross-titration between Soliris and Empaveli;*
   **Provider must submit attestation of the presence or absence of concomitant Soliris 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 [Preemptive Criteria]^ (must meet all)**:***
^Preemptive policy: This is a P&T approved policy and these criteria can be used after the drug is FDA-approved until it is superseded by an updated policy
**Criteria will mirror the clinical information from the prescribing information once FDA-approved*

1. Diagnosis of GA with all of the following characteristics (a, b, c, d, and e):*
   a. GA is secondary to AMD;
   b. Total GA area ≥ 2.5 and ≤ 17.5 mm^2 (1 and 7 disk areas [DA] respectively);
   c. If GA is multifocal, at least one focal lesion ≥ 1.25 mm^2 (0.5 DA);
   d. GA lesion(s) are not contiguous with any areas of peripapillary atrophy;

e. Presence of hyperautofluorescence in the junctional zone of GA;
2. Request is for APL-2;
3. Prescribed by or in consultation with an ophthalmologist;
4. Age ≥ 60 years;*
5. Best corrected visual acuity of 24 letters or better on Early Treatment Diabetic Retinopathy Study (ETDRS) charts (approximately 20/320 Snellen equivalent);*
6. 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);
7. APL-2 is not prescribed concurrently with Empaveli;
8. Dose does not exceed 15 mg per month in each affected eye.*

Approval duration: 12 months

C. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions 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 any of the following parameters (a – f):
   a. Improved measures of intravascular hemolysis (e.g., normalization of lactate dehydrogenase);
   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. APL-2;
   b. Another FDA-approved product for PNH (e.g., Soliris, Ultomiris);
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 months

B. Geographic Atrophy [Preemptive Criteria]^ (must meet all)**:***

^Preemptive policy: This is a P&T approved policy and these criteria can be used after the drug is FDA-approved until it is superseded by an updated policy
**Criteria will mirror the clinical information from the prescribing information once FDA-approved*

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Request is for APL-2;
3. Member is responding positively to therapy;
4. APL-2 is not prescribed concurrently with Empaveli;
5. If request is for a dose increase, new dose does not exceed 15 mg per month in each affected eye.*

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AMD: age-related macular degeneration
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; patients who are not currently vaccinated against certain encapsulated bacteria unless the risks of delaying Empaveli treatment outweigh the risks of developing a serious bacterial infection with an encapsulated organism; patients with unresolved serious infection caused by encapsulated bacteria
  - APL-2: pending
- 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)
  - APL-2: pending

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Empaveli	PNH	1,080 mg by SC infusion twice weekly via a commercially available pump For patients switching from Soliris, initiate Empaveli while continuing Soliris at its current dose. After 4 weeks, discontinue Soliris 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

Drug Name	Indication	Dosing Regimen	Maximum Dose
APL-2	GA*	Pending: 15 mg via intravitreal injection every month or every other month*	Pending: 15 mg/month*

VI. Product Availability

Drug Name	Availability
Empaveli	Single-dose vial for subcutaneous injection: 1,080 mg/20 mL
APL-2	Pending: Intravitreal injection: 15 mg/1 mL*

VII. References

1. Empaveli Prescribing Information. Waltham, MA: Apellis Pharmaceuticals, Inc.; May 2021. Available at: https://pi.apellis.com/files/PI_Empaveli.pdf. Accessed November 9, 2021.
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. Available at: https://apellis.com/presentations/2018%20-%20ASH%20poster%20PNH.pdf.
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 July 27, 2022.
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 July 27, 2022.
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 July 27, 2022.
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 July 27, 2022.
12. American Academy of Ophthalmology Retina/Vitreous Committee. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration. San Francisco, CA: American Academy of Ophthalmology; 2019. Available at: https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp. Accessed July 27, 2022.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	01.05.21	02.21
Drug is now FDA-approved – criteria updated per FDA labeling: modified restriction against concomitant use of Empaveli with Soliris by making an exception for the initial 4-week cross-titration phase; references reviewed and updated.	05.18.21	08.21
1Q 2022 annual review: increased the maximum recommended dose to accommodate patients who experience increased LDH levels, per dosing recommendations in the Empaveli PI; removed the requirement for initial approval for at least one RBC transfusion in the last 12 months since 25% of the patients in the PEGASUS trial had zero past transfusions and data from the trial did not show a difference in Empaveli effect for those patients; references reviewed and updated.	11.16.21	02.22
Added pre-emptive criteria for intravitreal pegcetacoplan (APL-2) for GA secondary to AMD.	07.27.22	11.22

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.