

Clinical Policy: Pegcetacoplan (Empaveli, APL-2)

Reference Number: CP.PHAR.524

Effective Date: 05.14.21

Last Review Date: 02.23

Line of Business: Commercial, HIM, Medicaid

[Coding Implications](#)

[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.

It is the policy of health plans affiliated with Centene Corporation[®] 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 \geq 18 years;
5. Flow cytometry shows detectable glycosylphosphatidylinositol (GPI)-deficient hematopoietic clones or \geq 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;*
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policy: This is a P&T approved policy and these criteria can be used after the drug is FDA-approved until it is superseded by an updated policy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 mm² (1 and 7 disk areas [DA] respectively);
 - c. If GA is multifocal, at least one focal lesion ≥ 1.25 mm² (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 (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 of the following policies (a or b):
 - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
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: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Paroxysmal Nocturnal Hemoglobinuria (must meet all):

1. Member meets one of the following (a or b):
 - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;

- b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
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. Member meets one of the following (a or b):
 - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
 - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
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. 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 of the following policies (a or b):
 - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

- b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
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: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, 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
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/0.1 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 3, 2022.
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 November 3, 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 November 3, 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 November 3, 2022.
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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 November 3, 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 November 3, 2022.

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
C9399	Unclassified drugs or biologicals
J7799	Noc drugs, other than inhalation drugs, administered through dme

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	11.16.21	02.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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.		
Added pre-emptive criteria for intravitreal pegcetacoplan (APL-2) for GA secondary to AMD. Template changes applied to other diagnoses/indications and continued therapy section.	07.27.22	11.22
1Q 2023 annual review: no significant changes; revised tentative product availability for APL-2 from 15 mg/1 mL to 15 mg/0.1 mL per manufacturer; references reviewed and updated.	11.03.22	02.23

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. The Health Plan 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. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:

For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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