Clinical Policy: Berotralstat (Orladeyo)

Reference Number: CP.PHAR.485
Effective Date: 12.03.20
Last Review Date: 08.25
Line of Business: Commercial*, Medicaid

Revision Log

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

Description

Berotralstat (Orladeyo®) is a plasma kallikrein inhibitor.

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** These criteria do NOT apply to California Exchange Plans. Requests for California Exchange Plans should be reviewed using HIM.PA.169.*

FDA Approved Indication(s)

Orladeyo is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 2 years and older.

Limitation(s) of use: The safety and effectiveness of Orladeyo for the treatment of acute HAE attacks have not been established. Orladeyo should not be used for treatment of acute HAE attacks. Additional doses or doses of Orladeyo higher than the prescribed once-daily dose are not recommended due to the potential for QTc interval prolongation.

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 Orladeyo is **medically necessary** when the following criteria are met:

1. Initial Approval Criteria

A. Hereditary Angioedema* (must meet all)**:**

** These criteria do NOT apply to California Exchange Plans. Requests for California Exchange Plans should be reviewed using HIM.PA.169.*

1. Diagnosis of HAE confirmed by a history of recurrent angioedema and one of the following (a or b):
   a. Low C4 level and low C1-INH antigenic or functional level (*see Appendix D*);
   b. Normal C4 level and normal C1-INH level, and at least one of the following (i or ii):
      i. Presence of a mutation associated with the disease (*see Appendix D*);
      ii. Family history of angioedema and documented failure of high-dose antihistamine therapy (i.e., cetirizine 40 mg/day or equivalent) for at least 1 month or an interval expected to be associated with 3 or more attacks of angioedema, whichever is longer;
2. Prescribed by or in consultation with an allergist, hematologist, or immunologist;
3. Age ≥ 2 years;

4. Prescribed for long-term prophylaxis of HAE attacks and request meets one of the following (a, b, or c);
   a. Member experiences more than one severe event per month;
   b. Member is disabled more than five days per month;
   c. Member has a history of previous airway compromise;
5. For members age ≥ 6 years: Failure of Haegarda®, unless contraindicated or clinically significant adverse effects are experienced;
6. Member is not using Orladeyo in combination with another FDA-approved product for long-term prophylaxis of HAE attacks (e.g., Cinryze®, Haegarda, Takhzyro®);
7. Dose does not exceed one of the following (a or b):
   a. Age ≥ 12 years: both of the following (i and ii):
      i. 150 mg per day;
      ii. 1 capsule per day;
   b. Age 2 to < 12 years: 1 oral pellet packet per day (*see weight-based dosing in Section V below*).

Approval duration: 6 months

B. 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 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 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 and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Hereditary Angioedema (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. Member is responding positively to therapy as evidenced by a reduction in attacks from baseline;
3. Member is not using Orladeyo in combination with another FDA-approved product for long-term prophylaxis of HAE attacks (e.g., Cinryze, Haegarda, Takhzyro);

4. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. Age ≥ 12 years: both of the following (i and ii):
      i. 150 mg per day;
      ii. 1 capsule per day;
   b. Age 2 to < 12 years: 1 oral pellet packet per day (*see weight-based dosing in Section V below*).

Approval duration: 12 months

B. 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 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 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 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 and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

C1-INH: C1 esterase inhibitor
C4: complement component 4
FDA: Food and Drug Administration
HAE: hereditary angioedema
HAE-nl-C1INH: hereditary angioedema with normal C1 inhibitor

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
cetirizine	40 mg/day (*off-label*) Typical dosing range (mg/day): 10 mg/day *US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema*	40 mg/day (*off-label*)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
C1 esterase inhibitor (Haegarda)	60 IU/kg body weight SC twice weekly (every 3 or 4 days)	Based on weight, 60 IU/kg/dose

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- Diagnosis of HAE:
  - There are two classifications of HAE: HAE with C1-INH deficiency (HAE-C1INH, further broken down into Type 1 and Type II) and HAE with normal C1-INH (also known as HAE-nl-C1INH). HAE-nl-C1INH was previously referred to as type III HAE, but this term is obsolete and should not be used.
  - In both Type 1 (~85% of cases) and Type II (~15% of cases), C4 levels are low. C1-INH antigenic levels are low in Type I while C1-INH functional levels are low in Type II. Diagnosis of Type I and II can be confirmed with laboratory tests. Reference ranges for C4 and C1-INH levels can vary across laboratories (see below for examples); low values confirming diagnosis are those which are below the lower end of normal.

Laboratory Test & Reference Range	Mayo Clinic	Quest Diagnostics	LabCorp
C4	14-40 mg/dL	13-57 mg/dL (age- and gender-specific ranges)	10-38 mg/dL (age- and gender-specific ranges)
C1-INH, antigenic	19-37 mg/dL	21-39 mg/dL	21-39 mg/dL
C1-INH, functional	Normal: > 67% Equivocal: 41-67% Abnormal: < 41%	Normal: ≥ 68% Equivocal: 41-67% Abnormal: ≤ 40%	Normal: > 67% Equivocal: 41-67% Abnormal: < 41%

  - HAE-nl-C1INH, on the other hand, presents with normal C4 and C1-INH levels. Some patients have a known associated mutation, while others have no identified genetic indicators. HAE-nl-C1INH is very rare, and there are no laboratory tests to confirm the diagnosis; mutations in 6 genes causing HAE-nl-C1INH have been identified:

Identified Genes Associated with Mutations in HAE-nl-C1INH
F12
ANGPT1
PLG
KNG1
MYOF
HS3ST6

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
HAE attack prophylaxis	Age ≥ 12 years (capsules): 150 mg PO QD Age 2 to < 12 years (oral pellets): PO QD • 12 kg to < 24 kg: 72 mg • 24 kg to < 32 kg: 96 mg • 32 kg to < 40 kg: 108 mg • ≥ 40 kg: 132 mg	150 mg/day

VI. Product Availability

- Capsules: 110 mg, 150 mg
- Unit-dose packets containing oral pellets: 72 mg, 96 mg, 108 mg, 132 mg

VII. References

1. Orladeyo Prescribing Information. Durham, NC: BioCryst Pharmaceuticals, Inc.; December 2025. Available at: https://orladeyo.com/. Accessed January 6, 2026.
2. Zuraw B, Lumry WR, Johnston DT, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: a randomized, double-blind, placebo-controlled phase 3 trial. *J Allergy Clin Immunol*. 2020; S0091-6749(20)31484-6. doi: 10.1016/j.jaci.2020.10.015.
3. Wedner HJ, Aygören-Pürsün E, Bernstein J, et al. Randomized trial of the efficacy and safety of berotralstat (BCX7353) as an oral prophylactic therapy for hereditary angioedema: Results of APeX-2 through 48 weeks (part 2). *J Allergy Clin Immunol Pract*. 2021 Jun;9(6):2305-2314.e4. doi: 10.1016/j.jaip.2021.03.057.
4. Farkas H, Stobiecki M, Peter J, et al. Long-term safety, and effectiveness of berotralstat for hereditary angioedema: The open-label APeX-S study. *Clin Transl Allergy*. 2021 Jun;11(4):e12035. doi: 10.1002/clt2.12035.
5. Ohsawa I, Honda D, Suzuki Y, et al. Oral berotralstat for the prophylaxis of hereditary angioedema attacks in patients in Japan: A phase 3 randomized trial. *Allergy*. 2021 Jun;76(6):1789-1799. doi: 10.1111/all.14670.
6. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.
7. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA medical advisory board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract.* 2020. https://doi.org/10.1016/j.jaip.2020.08.046.
8. Zuraw BL, Bork K, Bouillet L, et al. Hereditary angioedema with normal c1 inhibitor: an updated international consensus paper on diagnosis, pathophysiology, and treatment. *Clin Rev Allergy Immunol*. 2025 Mar 7;68(1):24. doi: 10.1007/s12016-025-09027-4.
9. Mayo Clinic Laboratories [internet database]. Rochester, Minnesota: May Foundation for Medical Education and Research. Updated periodically. Accessed April 25, 2025.
10. Quest Diagnostics® [internet database]. Updated periodically. Accessed April 25, 2025.
11. LabCorp [internet database]. Burlington, North Carolina: Laboratory Corporation of America. Updated periodically. Accessed April 25, 2025.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Per June SDC and prior clinical guidance, added redirection to Haegarda.	06.02.21	08.21
1Q 2022 annual review: updated diagnosis criteria to include a recurrent history of angioedema and either an associated mutation or family history of angioedema with failure of high-dose antihistamines for HAE-nl-C1INH; HIM line of business removed; references reviewed and updated.	11.03.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.03.22	
1Q 2023 annual review: no significant changes; updated Appendix D lab reference range and mutations associated with HAE; references reviewed and updated.	11.03.22	02.23
3Q 2023 annual review: HIM line of business added per HIM formulary status; references reviewed and updated.	04.21.23	08.23
Per August SDC, removed HIM line of business.	08.22.23	12.23
Per SDC, added the following clarification under the description and initial approval criteria sections: "These criteria do NOT apply to California Commercial Exchange Plans. Requests for California Commercial Exchange Plans should be reviewed using HIM.PA.169"	02.15.24	
3Q 2024 annual review: no significant changes; references reviewed and updated. Clarified that "California Commercial Exchange Plans" refers to "California Exchange Plans."	05.08.24	08.24
3Q 2025 annual review: no significant changes; updated FDA approved indication language to align with PI; references reviewed and updated.	04.25.25	08.25
RT4: updated to reflect pediatric extension down to 2 years of age and added new oral pellet dosage form.	01.06.26	

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.