Clinical Policy: Berotralstat (Orladeyo)

Reference Number: HIM.PA.169
Effective Date: 01.01.24
Last Review Date: 08.24
Line of Business: HIM

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.

FDA Approved Indication(s)

Orladeyo is indicated as prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older.

Limitation(s) of use: Orladeyo should not be used for treatment of acute HAE attacks.

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)**:**
     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 ≥ 12 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. Member is not using Orladeyo in combination with another FDA-approved product for long-term prophylaxis of HAE attacks (e.g., Cinryze®, Haegarda®, Takhzyro™);

6. Dose does not exceed both of the following (a and b):
   a. 150 mg per day;
   b. 1 capsule per day.

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: HIM.PA.33 for health insurance marketplace; 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: HIM.PA.103 for health insurance marketplace; 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: HIM.PA.154 for health insurance marketplace.

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 both of the following (a and b):
   a. 150 mg per day;
   b. 1 capsule per day.

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: HIM.PA.33 for health insurance marketplace; 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: HIM.PA.103 for health insurance marketplace; 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: HIM.PA.154 for health insurance marketplace.

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 – HIM.PA.154 for health insurance marketplace 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*)

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	150 mg PO QD	150 mg/day

VI. Product Availability

Capsules: 110 mg, 150 mg

VII. References

1. Orladeyo Prescribing Information. Durham, NC: BioCryst Pharmaceuticals, Inc.; November 2023. Available at: https://orladeyo.com/. Accessed May 8, 2024.
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. Mayo Clinic Laboratories [internet database]. Rochester, Minnesota: May Foundation for Medical Education and Research. Updated periodically. Accessed May 8, 2024.
9. Quest Diagnostics® [internet database]. Updated periodically. Accessed May 8, 2024.
10. LabCorp [internet database]. Burlington, North Carolina: Laboratory Corporation of America. Updated periodically. Accessed May 8, 2024.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created per August SDC (adapted from CP.PHAR.485).	08.22.23	12.23
3Q 2024 annual review: no significant changes; references reviewed and updated.	05.08.24	08.24

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.

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