Clinical Policy: Berotralstat (Orladeyo)

Reference Number: CP.PHAR.485
Effective Date: 12.03.20
Last Review Date: 08.21
Line of Business: Commercial, HIM, 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.

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:

I. Initial Approval Criteria

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

1. Diagnosis of HAE confirmed by 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 both of the following (i and ii):
      i. History of recurrent angioedema;
      ii. Family history of angioedema;
2. Prescribed by or in consultation with an allergist, hematologist, or immunologist;
3. Age ≥ 12 years;
4. Member 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. 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 150 mg (1 capsule) per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
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 150 mg (1 capsule) per day.

Approval duration: 12 months

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): 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
C1-INH: C1 esterase inhibitor
FDA: Food and Drug Administration
HAE: hereditary angioedema

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
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 (further broken down into Type 1 and Type II) and HAE of unknown origin (also known as Type III).
  - 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	16-47 mg/dL	13-44 mg/dL
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%

  - Type III, on the other hand, presents with normal C4 and C1-INH levels. Some patients have an associated mutation in the FXII gene, while others have no identified genetic indicators. Type III is very rare (number of cases unknown), and there are no laboratory tests to confirm the diagnosis. Instead, the diagnosis is clinical and supported by recurrent episodes of angioedema with a strong family history of angioedema.

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.; December 2020. Available at: https://www.biocryst.com/wp-content/uploads/2020/12/ORLADEYO_PI_V1_2020.pdf. Accessed December 8, 2020.
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. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03485911, Efficacy and Safety Study of BCX7353 as an Oral Treatment for the Prevention of Attacks in HAE (APeX-2); 16 December 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT03485911. Accessed March 30, 2020.
4. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03472040, A Long Term Safety Study of BCX7353 in Hereditary Angioedema (APeX-S); 18 March 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT03472040. Accessed March 30, 2020.
5. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03873116, Study to Evaluate the Efficacy and Safety of BCX7353 as an Oral Treatment for the Prevention of HAE Attacks in Japan (APeX-J); 7 August 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT03873116. Accessed March 30, 2020.
6. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. Allergy. 2018; 73(8):1575-1596.
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 December 10, 2020.
9. Quest Diagnostics® [internet database]. Updated periodically. Accessed December 10, 2020.
10. LabCorp [internet database]. Burlington, North Carolina: Laboratory Corporation of America. Updated periodically. Accessed December 10, 2020.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	04.14.20	05.20
Drug is now FDA approved – criteria updated per FDA labeling, amended bypass in 1.b from low C4 to normal C4, updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); references reviewed and updated.	01.12.21	02.21
Per June SDC and prior clinical guidance, added redirection to Haegarda.	06.02.21	08.21

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.