Clinical Policy: Berotralstat (Orladeyo)

Reference Number: ERX.SPA.393
Effective Date: 12.03.20
Last Review Date: 02.22
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.

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.

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 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 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. Failure of Takhzyro™, 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 ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Hereditary Angioedema (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. 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 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

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 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*)
Takhzyro™ (Lanadelumab-fylo)	300 mg SC every 2 weeks A dosing interval of 300 mg every 4 weeks may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months	300 mg SC every 2 weeks

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)	14-44 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%

  - 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 4 genes causing HAE-nl-C1INH have been identified:

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

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://orladeyo.com/. Accessed October 28, 2021.
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 November 8, 2021.
9. Quest Diagnostics® [internet database]. Updated periodically. Accessed November 8, 2021.
10. LabCorp [internet database]. Burlington, North Carolina: Laboratory Corporation of America. Updated periodically. Accessed November 8, 2021.

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; references reviewed and updated.	01.12.21	02.21
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; added redirection to Takhzyro; added criteria to restrict combination use with other products for long term prophylaxis to continuation of therapy; references reviewed and updated.	11.11.21	02.22

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.