

ORLADEYO (berotralstat)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication

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

Limitations of Use: Orladeyo should not be used for treatment of acute HAE attacks

All other indications are considered experimental/investigational and not medically necessary.

II. CRITERIA FOR INITIAL APPROVAL

Authorization for 6 months may be granted for prevention of hereditary angioedema attacks in members 2 years of age or older when the following criteria is met:

- A. Medication is prescribed by, or in consultation with allergist/immunologist or a physician who specializes in the management of HAE
- B. Member has documented diagnosis of HAE type I or type II and meets one of the following:
 1. Documentation that the member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
 - i. C1 inhibitor (C1-INH) antigenic level is below the lower limit of normal as defined by the laboratory performing the test; OR
 - ii. Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test); OR
 2. Documentation that the member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
 - i. Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) pathogenic variant as confirmed by genetic testing, OR
 - ii. Member has a family history of angioedema and the member's angioedema was refractory to a trial of high-dose antihistamine therapy (e.g., cetirizine 40mg per day or the equivalent) for at least one month.
- A. Other causes of angioedema have been ruled out (e.g., angiotensin-converting enzyme inhibitor [ACE-I] induced an angioedema, angioedema related to an estrogen containing

- drug, allergic angioedema).
- B. Member requires long-term prophylactic treatment based on the provider's assessment of the patient's disease activity, quality of life, availability of health care resources, and/or failure to achieve adequate control by appropriate on-demand therapy [i.e., Ekterly (sebetralstat), Kalbitor (ecallantide), Icatibant, Ruconest (C1 esterase inhibitor) or Berinert (C1 esterase inhibitor), etc.]
 - C. Member will not use Orladeyo (berotralstat) concomitantly with Takhzyro (lanadelumab-flyo), Andembry (garadacimab-gxii), Cinryze (C1 esterase inhibitor), Orladeyo (berotralstat), Haegarda (C1 esterase inhibitor) or Dawnzera (donidalorsen)

III. CONTINUATION OF THERAPY

Authorization of 6 months may be granted for continuation of therapy when all of the following criteria are met:

- A. Documentation that the member meets the criteria for initial approval.
- B. Member has documentation of experiencing a significant reduction in frequency of attacks (e.g., $\geq 50\%$) since starting prophylactic treatment;
- C. Member has documentation of reduced the use of medications to treat acute attacks since starting treatment.

IV. QUANTITY LIMIT

- Orladeyo 110mg & 150mg: 1 capsule per day
- Orladeyo 72 mg, 96 mg, 108 mg & 132 mg: 1 oral pellet pack per day

V. REFERENCES

1. Orladeyo [package insert]. Durham, NC: BioCryst Pharmaceuticals, Inc.; February 2026. Accessed May 2026.
2. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update. *Allergy*. 2022 Jan 10. doi: 10.1111/all. 15214. Online ahead of print.
3. Henao MP, Kraschnewski J, Kelbel T, Craig T. Diagnosis and screening of patients with hereditary angioedema in primary care. *Therapeutics and Clin Risk Management*. 2016; 12: 701-711.
4. 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.
5. 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: In Practice*. 2021 Jan;9(1):132-150.e3.
6. Sharma J, Jindal AK, Banday AZ, et al. Pathophysiology of Hereditary Angioedema (HAE) Beyond the SERPING1 Gene [published online ahead of print, 2021 Jan 14] [published correction appears in Clin Rev Allergy Immunol. 2021 Feb 17]. *Clin Rev Allergy Immunol*. 2021;10.1007/s12016-021-08835-8. Doi:10.1007/s12016-021-08835-8.
7. Kanani, A., Schellenberg, R. & Warrington, R. Urticaria and angioedema. *All Asth Clin Immun* 7, S9 (2011), Table 2.