Effective date: 5/1/2021
Reviewed: 2/2021, 2/2022, 3/2023, 3/2024, 6/2025, 11/2025 Scope: Medicaid

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 12 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 12 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.
C. 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).

D. 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.]
E. 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., ≥ 50%) since starting prophylactic treatment.
C. Member has documentation of reduced use of medications to treat acute attacks since starting treatment.

IV. QUANTITY LIMIT

Orladeyo 110mg & 150mg: 1 capsule per day

V. REFERENCES

1. Orladeyo [package insert]. Durham, NC: BioCryst Pharmaceuticals, Inc.; October 2024.Accessed October 2025.
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.

Effective date: 5/1/2021
Reviewed: 2/2021, 2/2022, 3/2023, 3/2024, 6/2025, 11/2025 Scope: Medicaid