UnitedHealthcare Pharmacy
Clinical Pharmacy Programs

Program Number	2026 P 2232-9
Program	Prior Authorization/Medical Necessity
Medication	Orladeyo® (berotralstat)*
P&T Approval Date	3/2021, 8/2021, 10/2021, 10/2022, 10/2023, 3/2024, 3/2025, 11/2025, 1/2026
Effective Date	4/1/2026

1. Background:

Orladeyo is a plasma kallikrein inhibitor indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 2 years and older. Orladeyo should not be used for the treatment of acute HAE attacks.[1]

2. Coverage Criteria[a]:

A. Orladeyo* will be approved based on **all** of the following criteria:

1. Diagnosis of hereditary angioedema (HAE) as confirmed by **one** of the following:

   a. C1 inhibitor (C1-INH) deficiency or dysfunction (Type I or II HAE) as documented by **one** of the following (per laboratory standard):

      (1) C1-INH antigenic level below the lower limit of normal

      (2) C1-INH functional level below the lower limit of normal

-OR-

   b. HAE with normal C1 inhibitor levels and **one** of the following:

      (1) Confirmed presence of variant(s) in the gene(s) for factor XII, angiopoietin-1, plasminogen-1, kininogen-1, myoferlin, and heparan sulfate-glucosamine 3-O-sulfotransferase 6

      (2) Recurring angioedema attacks that are refractory to high-dose antihistamines with confirmed family history of angioedema

      (3) Recurring angioedema attacks that are refractory to high-dose antihistamines with unknown background de-novo mutation(s) (i.e., no family history) (HAE-unknown)

-AND-

2. Prescribed for the prophylaxis of HAE attacks

-AND-

3. Not used in combination with other approved products indicated for prophylaxis against HAE attacks (i.e., Andembry, Cinryze, Dawnzera, Haegarda, Takhzyro)

-AND-

4. Prescriber attests that patient has experienced attacks of a severity and/or frequency such that they would clinically benefit from prophylactic therapy with Orladeyo

-AND-

5. **One** of the following:

   a. **Both** of the following:

      (1) Patient is greater than or equal to 2 years of age and less than 6 years of age

      -AND-

      (2) History of failure to Takhzyro (lanadelumab) (document date of trial and list reason for therapeutic failure)

      -OR-

   b. **Both** of the following:

      (1) Patient is greater than or equal to 6 years of age and less than 12 years of age

      -AND-

      (2) History of failure to **both** of the following (document date of trial and list reason for therapeutic failure):

         (a) Haegarda (C1 esterase inhibitor, human)

         (b) Takhzyro (lanadelumab)

      -OR-

   c. **Both** of the following:

      (1) Patient is greater than or equal to 12 years of age

      -AND-

      (2) History of failure to **all** of the following (document date of trial and list reason for therapeutic failure):

         (a) Andembry (garadacimab)

         (b) Haegarda (C1 esterase inhibitor, human)

(c) Takhzyro (lanadelumab)

-AND-

6. Prescribed by **one** of the following:

   a. Immunologist

   b. Allergist

Authorization will be issued for 12 months.

[a] State mandates may apply. Any federal regulatory requirements and the member specific benefit plan coverage may also impact coverage criteria. Other policies and utilization management programs may apply.

* Orladeyo is typically excluded from coverage. Coverage reviews may be in place if required by law or the benefit plan.

3. Additional Clinical Rules:

- Notwithstanding Coverage Criteria, UnitedHealthcare may approve initial and re-authorization based solely on previous claim/medication history, diagnosis codes (ICD-10) and/or claim logic. Use of automated approval and re-approval processes varies by program and/or therapeutic class.
- Supply limits may be in place.

4. References:

1. Orladeyo [package insert]. Durham, NC: BioCryst Pharmaceuticals Inc.; December 2025.
2. Busse, P., Christiansen, S., Riedl, M., et. al. "US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema." *The Journal of Allergy and Clinical Immunology.* 2020 September 05.
3. Maurer, M., Magerl, M., et. al. "The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update." *World Allergy Organization Journal.* 2018 February 27.

Program	Prior Authorization/Medical Necessity – Orladeyo (berotralstat)
Change Control	
3/2021	New program.
8/2021	Criteria updated to include failure of both Haegarda and Takhzyro. Reauthorization criteria removed. Exclusion statement added.
10/2021	Removed Initial Authorization verbiage and updated formatting with no change to clinical criteria.
10/2022	Annual review with no changes to clinical criteria. Updated reference.
10/2023	Annual review with no changes to clinical criteria.

3/2024	Annual review with update to diagnostic criteria for HAE with normal C1 inhibitor levels.
3/2025	Annual review with no changes to clinical criteria. Updated reference.
11/2025	Updated coverage criteria by adding Andembry to list of required preventive HAE agents. Updated examples of prophylactic HAE drugs to include Andembry and Dawnzera.
1/2026	Updated coverage criteria based on updated FDA indication by separating tried/failed therapies based on age limitations for Haegarda and Andembry. Updated background and references.