



Drug Coverage Policy

Effective Date03/01/2026

Coverage Policy Number.....IP0096

Policy Title..... Orladeyo

Hereditary Angioedema - Orladeyo

- Orladeyo® (berotralstat capsules and oral pellets – Biocryst)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Orladeyo, an inhibitor of plasma kallikrein, is indicated for **prophylaxis to prevent attacks of hereditary angioedema (HAE)** in adults and pediatric patients ≥ 2 years of age.¹

The safety and effectiveness of Orladeyo for the treatment of acute HAE attacks have not been established, so Orladeyo should not be used for treatment of acute HAE attacks.¹ Due to QTc interval prolongation, additional doses or doses higher than the prescribed once-daily dose are not recommended.

Clinical Efficacy

The efficacy of Orladeyo for the prevention of HAE attacks in adult and pediatric patients 12 years of age and older with type I or type II HAE was demonstrated in a randomized, double-blind, placebo-controlled, parallel-group trial, APeX-2.¹ Although the FDA-approved indication for Orladeyo does not specify HAE type I or type II, the APeX-2 study inclusion criteria required a diagnosis of HAE type I or II, as confirmed by C1 esterase inhibitor functional level and C4 levels.²

Guidelines

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1 esterase inhibitor (C1-INH) antigenic level, and C1-INH functional level.³ Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The decision on when to use long-term prophylaxis cannot be made on rigid criteria but should reflect the needs of the individual patient. First-line medications for HAE I/II include intravenous C1-INH, Haegarda® (C1-INH [human] subcutaneous injection), or Takhzyro® (lanadelumab-flyo subcutaneous injection). The guidelines note that HAE with normal C1-INH (HAE-nC1INH) is challenging to diagnose due to the lack of validated biochemical test. Genetic testing could be helpful in confirming diagnosis. The guideline was written prior to the approval of Orladeyo.

According to World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2021), it is recommended to evaluate for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration.⁴ The following therapies are supported as first-line options for long-term prophylaxis: plasma-derived C1-INH (87% agreement), Takhzyro (89% agreement), and Orladeyo (81% agreement). With regard to plasma-derived C1-INH, it is noted that Haegarda provided very good and dose-dependent preventative effects on the occurrence of HAE attacks; the subcutaneous route may provide more convenient administration and maintains improved steady-state plasma concentrations compared with the intravenous route. Of note, androgens are not recommended in the first-line setting for long-term prophylaxis. Recommendations are not made regarding long-term prophylaxis in HAE with normal C1-INH levels.

An international consensus paper was published on the diagnosis, pathophysiology, and treatment of HAE-nl-C1INH.⁵ The paper notes there is a paucity of high-level evidence in HAE-nC1INH and that all recommendations are based on expert opinion. There are very limited data with Orladeyo use for HAE-nl-C1INH. The consensus paper notes that icatibant and plasma-derived C1-INH therapies have been used for on-demand acute treatment; progestins, tranexamic acid, and androgens are reported as the most used long-term prophylaxis treatments.

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POLICY STATEMENT

Prior Authorization is required for benefit coverage of Orladeyo. Because of the specialized skills required for evaluation and diagnosis of patients treated with Orladeyo, approval requires Orladeyo to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met initial therapy criteria for Orladeyo for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., currently receiving Orladeyo). If past criteria have not been met under the Coverage Review Department

and the patient is currently receiving Orladeyo, initial therapy criteria must be met. All approvals are provided for the duration noted below.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records. All documentation must include patient-specific identifying information.

Orladeyo is considered medically necessary when the following are met:

FDA-Approved Indication

1. Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency -

Prophylaxis. Approve for 1 year if the patient meets ONE of the following (A or B):

A. Initial therapy. Approve if the patient meets ALL of the following (i, ii, and iii):

- i.** Patient is ≥ 2 years of age; AND
- ii.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
Note: A diagnosis of HAE with normal C1-INH (also referred to as HAE type III) does NOT satisfy this requirement.
 - a.** Patient has low levels of functional C1-INH protein ($< 50\%$ of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
 - b.** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
- iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

B. Patient is currently receiving Orladeyo. Approve if the patient meets ALL of the following (i, ii, and iii):

Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Orladeyo for this indication through the Coverage Review Department, review under criteria for Initial Therapy.

- i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
Note: A diagnosis of HAE with normal C1-INH (also referred to as HAE type III) does NOT satisfy this requirement.
- ii.** According to the prescriber, the patient has had a favorable clinical response since initiating Orladeyo prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND
Note: Examples of favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.
- iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

Conditions Not Covered

Orladeyo for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. Concomitant Use with Other Hereditary Angioedema (HAE) Prophylactic Therapies.

Note: Examples of other HAE prophylactic therapies include Cinryze (C1 esterase inhibitor [human] intravenous infusion), Haegarda (C1 esterase inhibitor [human] subcutaneous injection), and Takhzyro (lanadelumab-flyo subcutaneous injection).

Orladeyo has not been studied in combination with other prophylactic therapies for HAE, and combination therapy for long-term prophylactic use is not recommended. Patients may use other medications, including Cinryze, for on-demand treatment of acute HAE attacks, and for short-term (procedural) prophylaxis.

References

1. Orladeyo® capsules [prescribing information]. Durham, NC: Biocryst; December 2025.
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.* 2021;148(1):164-172.e9.
3. 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.* 2021;9(1):132-150.e3.
4. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy.* 2022;77(7):1961-1990.
5. Zuraw BL, Bork K, Bouillet L, et al. Hereditary angioedema with normal C1 inhibitor: an updated international consensus paper on diagnosis, pathophysiology, and treatment. *Clin Rev Allergy Immunol.* 2025;68:24.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes	1/1/2025
Annual Revision	<p>Policy Title. Updated from "Hereditary Angioedema - Berotralstat" to "Hereditary Angioedema - Orladeyo"</p> <p>Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency - Prophylaxis Added "Due to C1 Inhibitor (C1-INH) Deficiency" to indication name Added "Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b): Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement." Removed "Confirmed pathogenic variant in the <i>SERPING1, F12, ANGPT1, PLG</i> or <i>KNG1</i> gene" Removed "Has low C1-INH antigenic levels (less than 50% of normal) at baseline, as documented by laboratory reference values" Added "a physician who specializes in the treatment of HAE or related disorders" to specialist requirement.</p>	1/1/2026

	Added criteria for Patients currently receiving Orladeyo	
Selected Revision	<p>Added Orladeyo oral pellets (new formulation) to the policy with the same requirements applied as the tablets.</p> <p>Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis: Under Initial Therapy, patient age requirement was changed from ≥ 12 years of age to ≥ 2 years of age.</p>	03/01/2026

The policy effective date is in force until updated or retired.

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