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Section:	Prescription Drugs	**Effective Date:**	January 9, 2026
Subsection:	Hematological Agents	**Original Policy Date:**	January 22, 2021
Subject:	Orladeyo	**Page:**	1 of 4

Last Review Date: September 19, 2025

Orladeyo

Description

Orladeyo (berotralstat)

Background

Orladeyo (berotralstat) is a plasma kallikrein inhibitor that binds plasma kallikrein and inhibits its proteolytic activity. Plasma kallikrein is a protease that cleaves high-molecular-weight-kininogen (HMWK) to generate cleaved HMWK (cHMWK) and bradykinin, a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with hereditary angioedema (HAE). In patients with HAE due to C1-inhibitor deficiency or dysfunction, normal regulation of plasma kallikrein activity is not present, which leads to uncontrolled increases in plasma kallikrein activity and results in angioedema attacks. Orladeyo decreases plasma kallikrein activity to control excess bradykinin generation in patients with HAE (1).

Regulatory Status

FDA-approved indication: Orladeyo is a plasma kallikrein inhibitor indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older (1).

Limitations of use: Orladeyo should not be used for treatment of acute HAE attacks (1).

Additional doses or doses of Orladeyo higher than 150 mg once daily are not recommended. An increase in QT was observed at dosages higher than the recommended 150 mg once daily dosage and was concentration dependent (1).

The safety and effectiveness of Orladeyo in pediatric patients less than 12 years of age have not been established (1).

Related policies
Berinert, Cinryze, Haegarda, Icatibant, Kalbitor, Ruconest, Takhzyro

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Orladeyo may be considered **medically necessary** if the conditions indicated below are met.

Orladeyo may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 12 years of age and older

Diagnosis

Patient must have the following:

1. Hereditary Angioedema (HAE) with **ONE** of the following:
    a. Patient has a C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing **AND ALL** of the following:
        i. C4 level below the lower limit of normal as defined by the laboratory performing the test
        ii. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test **OR** 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)
    b. Patient has normal C1 inhibitor as confirmed by laboratory testing **AND ONE** of the following:
        i. F12, angiopoietin-1, plasminogen, or kininogen-1 (KNG1) gene mutation as confirmed by genetic testing
        ii. Documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (e.g.,

cetirizine) for at least one month

AND ALL of the following:

1. Used for the routine prevention of hereditary angioedema attacks
2. **NO** dual therapy with other agents for the prevention of hereditary angioedema attacks (e.g., Cinryze, Haegarda, Takhzyro)

Prior – Approval *Renewal* Requirements

Age 12 years of age and older

Diagnosis

Patient must have the following:

Hereditary Angioedema (HAE)

AND ALL of the following:

1. Used for the routine prevention of hereditary angioedema attacks
2. Patient has experienced a significant reduction in frequency of hereditary angioedema attacks since starting treatment
3. **NO** dual therapy with other agents for the prevention of hereditary angioedema attacks (e.g., Cinryze, Haegarda, Takhzyro)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity 84 capsules per 84 days

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary
Orladeyo (berotralstat) is a plasma kallikrein inhibitor that binds plasma kallikrein and inhibits its proteolytic activity. Plasma kallikrein is a protease that cleaves high-molecular-weight-kininogen (HMWK) to generate cleaved HMWK (cHMWK) and bradykinin, a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with hereditary angioedema (HAE). In patients with HAE due to C1-inhibitor deficiency or dysfunction, normal regulation of plasma kallikrein activity is not present, which leads to uncontrolled increases in plasma kallikrein activity and results in angioedema attacks. Orladeyo decreases plasma kallikrein activity to control excess bradykinin generation in patients with HAE (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Orladeyo while maintaining optimal therapeutic outcomes.

References

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

Policy History

Date	Action
January 2021	Addition to PA
March 2021	Annual editorial review
April 2021	Added initiation requirements including C1 inhibitor testing, C4 testing, C1-INH testing, gene mutation testing, or documented family history of refractory angioedema and continuation requirement for significant reduction in frequency of HAE attacks since starting therapy per FEP
June 2021	Annual review
September 2022	Annual review and reference update
September 2023	Annual review
December 2023	Annual review
September 2024	Annual review and reference update
December 2024	Annual review
September 2025	Annual review and reference update
January 2026	Per SME, removed initiation requirement to t/f a short term course of an androgen

Keywords

This policy was effective with interim approval on January 9, 2026 and will be reviewed by the FEP® Pharmacy and Medical Policy Committee on March 6, 2026.