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Coverage Policy Number **IP0096**

Hereditary Angioedema - Berotralstat

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Related Coverage Resources

Genetic Testing for Hereditary and Multifactorial Conditions

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. 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

This policy supports medical necessity review for berotralstat capsules (**Orladeyo**®).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Berotralstat (Orladeyo) is considered medically necessary when the following are met:

Hereditary Angioedema (HAE) - Prophylaxis. Individual meets **ALL** of the following criteria:
A. Age 12 years or older
B. Diagnosis of HAE confirmed by documentation of **ONE** of the following:
   i. Confirmed monoallelic pathogenic variant in the *SERPING1*, *F12*, *ANGPT1*, *PLG* or *KNG1* gene
   ii. One C4 level below the lower limit of normal as defined by the laboratory performing the test and **ONE** of the following:

a. Has low levels of functional C1 inhibitor (C1-INH) protein (less than 50% of normal) at baseline, as documented by laboratory reference values
b. Has low C1-INH antigenic levels (less than 50% of normal) at baseline, as documented by laboratory reference values

C. Medication is prescribed by, or in consultation with, an allergist/immunologist

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When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of berotralstat (Orladeyo) is considered medically necessary for hereditary angioedema prophylaxis when **ALL** of the following are met:

1. The above medical necessity criteria have been met prior to the start of Orladeyo therapy
2. There is documentation of beneficial response since initiating Orladeyo prophylactic therapy compared with baseline (for example, decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks)
3. Medication continues to be prescribed by, or in consultation with, an allergist/immunologist

Authorization Duration

Initial approval duration: up to 12 months.
Reauthorization approval duration: up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

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

Background

OVERVIEW
Orladeyo, an inhibitor of plasma kallikrein, is indicated for **prophylaxis to prevent attacks of hereditary angioedema (HAE)** in patients ≥ 12 years of age.[1]

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.[2] 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 guideline was written prior to 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.[3] 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.

References

1. Orladeyo® capsules [prescribing information]. Durham, NC: Biocryst; December 2020.
2. 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.
3. 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.