Cigna National Preferred Formulary Coverage Policy

Prior Authorization
Hereditary Angioedema - Orladeyo™ (berotralstat capsules)

Table of Contents
NPF Coverage Policy ..........................................1
Background..........................................................2
References ..........................................................3
Last Revision Details .................................3

Related Coverage Resources

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.

NPF Coverage Policy

Cigna covers berotralstat (Orladeyo™) as medically necessary when the following criteria are met for FDA Indications or Other Uses with Supportive Evidence:

Prior Authorization is recommended for prescription benefit coverage of Orladeyo. Because of the specialized skills required for evaluation and diagnosis of individuals with this condition, approval requires Orladeyo to be prescribed by or in consultation with a physician who specializes in the condition being treated. 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.

FDA Indication(s)
1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis.** Approve Orladeyo for the duration noted if the individual meets one the following criteria (A or B):

   **A) Initial therapy.** Approve for 1 year if the individual meets the following criteria (i, ii, and iii):
   
   i. Individual is ≥ 12 years of age; AND
   
   ii. Individual has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
   
   a) Individual has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values [documentation required]; AND
   
   b) Individual 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) Individual is currently receiving Orladeyo.** Approve for 1 year if the individual meets all of the following criteria (i, ii, iii, and iv):
   
   i. Individual is ≥ 12 years of age; AND
   
   ii. Individual has a diagnosis of HAE type I or II [documentation required]; AND
   
   iii. According to the prescriber, the individual 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.
   
   iv. 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**

Berotralstat (Orladeyo™) is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all inclusive):

**1. Concomitant Use with Other HAE Prophylactic Therapies (e.g., Cinryze®, Haegarda®, Takhzyro).**

Orladeyo has not been studied in combination with other prophylactic therapies for HAE, and combination therapy for long-term prophylactic use is not recommended. Individuals 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

**Disease Overview**

HAE due to C1 esterase inhibitor (C1-INH) deficiency has two subtypes: HAE type I and HAE type II. HAE diagnosis can be confirmed by measuring functional C1-INH protein levels (usually < 50% of normal in patients with HAE), C4 levels, and C1-INH antigenic levels.²⁻³ Patients with HAE type I have low C4 and C1-INH antigenic protein levels, along with low levels of functional C1-INH protein. Patients with HAE type II have low C4 and functional C1-INH protein level, with a normal or elevated C1-INH antigenic protein level. C1-INH replacement therapies are appropriate for both HAE type I and type II.

Patients with the third type of HAE called HAE with normal C1-INH (HAE nC1-INH), previously referred to as HAE type III, have normal C4 and C1-INH antigenic protein levels.² HAE nC1-INH is much less prevalent than HAE types I/II, and the exact cause of HAE nC1-INH has not been determined.²⁻⁴ Pathogenic variants in the genes encoding for Factor XII (regulates bradykinin generation), angiopoietin-1 (involved in vascular permeability), and plasminogen have been associated with HAE nC1-INH; however, the majority of cases have
unknown etiology. There are no randomized or controlled clinical trial data available with any therapy for use in HAE nC1-INH.4-6

Guidelines
Orladeyo is not yet addressed in guideline recommendations, although positive Phase III data are recognized in 2020 guidelines from the US HAE Association Medical Advisory Board.8 Per guidelines, the decision to initiate long-term prophylaxis is individualized based on multiple factors and should be made by the patient and an HAE specialist.4,8 C1-INH concentrate and Takhzyro™ (lanadelumab-flyo subcutaneous injection) are recognized as first-line treatment options for long-term prophylaxis of HAE type I/II attacks.3,4,8 Androgens are not considered first-line and are contraindicated in certain groups (e.g., pregnancy, prepubescent children, androgen-dependent malignancy).4 In other populations, the use of androgens for long-term prophylaxis may be considered as second-line but should be considered critically due to potential for adverse events. Therefore, guidelines note that androgens should not be used in patients who have a preference for alternative therapy and that patients should not be required to fail anabolic androgen therapy as a prerequisite to receiving prophylactic C1-INH or Takhzyro therapy.4,7 Of note, long-term prophylaxis for patients with HAE with normal C1-INH has not been studied in a randomized, placebo-controlled trial; hormonal therapy and antifibrinolytics are generally used for prophylaxis in this scenario.8

References

Last Revision Details

| New Policy | 12/09/2020 |

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