Berotralstat

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Overview

This policy supports medical necessity review for Orladeyo™ (berotralstat).

Medical Necessity Criteria

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

1. **Prophylaxis against angioedema attacks related to Hereditary Angioedema (HAE).** Individual meets ALL of the following criteria:
   A. Individual is 12 years of age or older
   B. Individual has HAE as confirmed by EITHER of the following:
      i. Confirmed monoallelic mutation known to cause HAE in either the SERPING1 or F12 gene
      ii. One C4 level below the lower limit of normal as defined by the laboratory performing the test and EITHER of the following:
a. C1 inhibitor (C1INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test
b. C1INH functional level below the lower limit of normal as defined by the laboratory performing the test
C. Medication is being prescribed by, or in consultation with, an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders

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.

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

### Reauthorization Criteria

Berotralstat (Orladeyo) is considered medically necessary for continued use when initial criteria are met AND documentation of beneficial response.

**Note:** Examples of beneficial response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.

### Authorization Duration

Initial approval duration is up to 12 months.

Reauthorization approval duration is up to 12 months.

### 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. 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

**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.²³ 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.²⁴ 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