MEDICAL MUTUAL®

Drug Policy

Policy:	Orladeyo (berotralstat)	Annual Review Date: 01/16/2025 Last Revised Date: 01/16/2025

OVERVIEW

Orladeyo is a plasma kallikrein inhibitor that binds to plasma kallikrein and inhibits its proteolytic activity. In patients with hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) 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.

POLICY STATEMENT

This policy involves the use of Orladeyo. Prior authorization is recommended for pharmacy benefit coverage of Orladeyo. Approval is recommended for those who meet the conditions of coverage in the **Criteria and Initial/Extended Approval** for the diagnosis provided. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Orladeyo as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Orladeyo be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Orladeyo is recommended in those who meet the following criteria:

1. <u>Hereditary Angioedema [Type I or Type II]; Prophylaxis</u>
Patient must meet the following criteria (a, b, c, d, e, f, and g):

a) Patient is 12 years of age or older; AND
b) The patient has HAE as confirmed by the following criteria (i <u>or</u> ii):
   i. Patient has low levels of functional C1-INH protein (below 50% of normal) at baseline, as defined by the laboratory reference values*; OR
   ii. Patient has lower than normal serum C4 levels (< 14 mg/dL) at baseline, as defined by the laboratory reference values AND lower than normal C1-INH levels (< 19.9 mg/dL) at baseline, as defined by the laboratory reference values*; AND

c) The medication is prescribed by or in consultation with an allergist, immunologist, hematologist or a physician that specializes in the treatment of HAE or related disorders; AND

2. **Patient has been started on Orladeyo.**
Patient must meet the following criteria (a, b, c, d, e, f, g, h, i, and j):
   a) Patient is 12 years of age or older; AND
   b) The patient has HAE as confirmed by the following criteria (i or ii):
      i. Patient has low levels of functional C1-INH protein (below 50% of normal) at baseline, as defined by the laboratory reference values*; OR
      ii. Patient has lower than normal serum C4 levels (< 14 mg/dL) at baseline, as defined by the laboratory reference values AND lower than normal C1-INH levels (< 19.9 mg/dL) at baseline, as defined by the laboratory reference values*; AND
   c) The medication is prescribed by or in consultation with an allergist, immunologist, hematologist or a physician that specializes in the treatment of HAE or related disorders; AND
      i.
      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.

Initial Approval/ Extended Approval.
A) *Initial Approval:* 1 year
B) *Extended Approval:* 1 year

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Orladeyo has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

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.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

***Documentation Requirements:**
The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a

pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

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3. Mauer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. Allergy. 2018;73(8):1575-1596.
4. Betschel S, Badiou J, Binkley K, et al. The International/Canadian Hereditary Angioedema Guideline [published correction appears in Allergy Asthma Clin Immunol. 2020 May 6;16:33]. Allergy Asthma Clin Immunol. 2019;15:72.
5. Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. Allergy Asthma Proc. 2012;33:S145-S156.
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7. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. J Allergy Clin Immunol: In Practice. 2013;1:458-467.
8. 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. 2020 Sep 6:S2213-2198(20)30878-3.