

Drug Policy

Policy:	Orladeyo (berotralstat)	Annual Review Date: 01/18/2024 Last Revised Date: 01/18/2024
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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. **Hereditary Angioedema [Type I or Type II]; Prophylaxis**

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 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 [documentation required]; 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 [documentation required]; AND

Drug Policy

- 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
- d) Patient has experienced treatment failure, intolerance, or has contraindication(s) to attenuated androgens (e.g, danazol, stanozolol) [documentation required]; AND
- e) All other causes of acquired angioedema (e.g., medications, auto-immune diseases) have been excluded; AND
- f) Patient has at least ONE of the following criteria (i, ii, or iii):
 - i. Patient has a history of one or more severe attack(s) per month (defined as an attack that significantly interrupts daily activities despite short-term treatment)
 - ii. Disabling symptoms for at least 5 days per month
 - iii. Laryngeal edema; AND
- g) Patient has at least ONE of the following criteria (i, ii, or iii)
 - i. Patient must have history of self-limiting, non-inflammatory subcutaneous angioedema, without urticaria, which is recurrent and lasts >12 hours
 - ii. Self-limiting, recurrent abdominal pain without a clear organic cause lasting >6 hours
 - iii. A history of laryngeal edema; AND

2. **Patient has been started on Orladevo.**

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 [documentation required]; 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 [documentation required]; 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
- d) Patient has experienced treatment failure, intolerance, or has contraindication(s) to attenuated androgens (e.g, danazol, stanozolol) [documentation required]; AND
- e) All other causes of acquired angioedema (e.g., medications, auto-immune diseases) have been excluded; AND
- f) Patient has at least ONE of the following criteria (i, ii, or iii):
 - i. Patient has a history of one or more severe attack(s) per month (defined as an attack that significantly interrupts daily activities despite short-term treatment)
 - ii. Disabling symptoms for at least 5 days per month
 - iii. Laryngeal edema; AND
- g) Patient has at least ONE of the following criteria (i, ii, or iii)
 - i. Patient must have history of self-limiting, non-inflammatory subcutaneous angioedema, without urticaria, which is recurrent and lasts >12 hours
 - ii. Self-limiting, recurrent abdominal pain without a clear organic cause lasting >6 hours
 - iii. A history of laryngeal edema
- h) Patient has at least 1 annual assessment by an HAE specialist if it has been one year since initial approval; AND

Drug Policy

- i) According to the prescriber, the patient has had a favorable clinical response (e.g., decrease in number of HAE acute attack frequency, decrease in HAE attack severity, decrease in duration of HAE attacks) since initiating Orladeyo prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND
- j) Reduction in the utilization of on-demand therapies used for acute attacks (e.g. Berinert, Ruconest, Firazyr, Kalbitor) as determined by claims information, while on Orladeyo therapy.

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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Drug Policy

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.
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