Clinical Policy: Berotralstat (Orladeyo)
Reference Number: CP.PHAR.485
Effective Date: 12.03.20
Last Review Date: 02.21
Line of Business: Commercial, HIM, Medicaid

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Berotralstat (Orladeyo™) is a plasma kallikrein inhibitor.

FDA Approved Indication(s)
Orladeyo is indicated as prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older.

Limitation(s) of use: Orladeyo should not be used for treatment of acute HAE attacks.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Orladeyo is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Hereditary Angioedema (must meet all):
      1. Diagnosis of HAE confirmed by one of the following (a or b):
         a. Low C4 level and low C1-INH antigenic or functional level (see Appendix D);
         b. Normal C4 level and normal C1-INH level, and both of the following (i and ii):
            i. History of recurrent angioedema;
            ii. Family history of angioedema;
      2. Prescribed by or in consultation with an allergist, hematologist, or immunologist;
      3. Age ≥ 12 years;
      4. Member meets one of the following (a, b, or c):
         a. Member experiences more than one severe event per month;
         b. Member is disabled more than five days per month;
         c. Member has a history of previous airway compromise;
      5. Member is not using Orladeyo in combination with another FDA-approved product for long-term prophylaxis of HAE attacks (e.g., Cinryze®, Haegarda®, Takhzyro™);
      6. Dose does not exceed 150 mg (1 capsule) per day.

   Approval duration: 6 months

   B. Other diagnoses/indications
      1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is
II. Continued Therapy
   A. Hereditary Angioedema (must meet all):
      1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
      2. Member is responding positively to therapy as evidenced by a reduction in attacks from baseline;
      3. Member is not using Orladeyo in combination with another FDA-approved product for long-term prophylaxis of HAE attacks (e.g., Cinryze, Haegarda, Takhzyro);
      4. If request is for a dose increase, new dose does not exceed 150 mg (1 capsule) per day.

   Approval duration: 12 months

   B. Other diagnoses/indications (must meet 1 or 2):
      1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
         Approval duration: Duration of request or 6 months (whichever is less); or
      2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:
   A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information
   Appendix A: Abbreviation/Acronym Key
   C1-INH: C1 esterase inhibitor
   FDA: Food and Drug Administration
   HAE: hereditary angioedema

   Appendix B: Therapeutic Alternatives
   Not applicable

   Appendix C: Contraindications/Boxed Warnings
   None reported

   Appendix D: General Information
   - Diagnosis of HAE:
     o There are two classifications of HAE: HAE with C1-INH deficiency (further broken down into Type I and Type II) and HAE of unknown origin (also known as Type III).
In both Type I (~85% of cases) and Type II (~15% of cases), C4 levels are low. C1-INH antigenic levels are low in Type I while C1-INH functional levels are low in Type II. Diagnosis of Type I and II can be confirmed with laboratory tests. Reference ranges for C4 and C1-INH levels can vary across laboratories (see below for examples); low values confirming diagnosis are those which are below the lower end of normal.

<table>
<thead>
<tr>
<th>Laboratory Test &amp; Reference Range</th>
<th>Mayo Clinic</th>
<th>Quest Diagnostics</th>
<th>LabCorp</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4</td>
<td>14-40 mg/dL</td>
<td>16-47 mg/dL</td>
<td>13-44 mg/dL</td>
</tr>
<tr>
<td>C1-INH, antigenic</td>
<td>19-37 mg/dL</td>
<td>21-39 mg/dL</td>
<td>21-39 mg/dL</td>
</tr>
<tr>
<td>C1-INH, functional</td>
<td>Normal: &gt; 67%</td>
<td>Normal: ≥ 68%</td>
<td>Normal: &gt; 67%</td>
</tr>
<tr>
<td></td>
<td>Equivocal: 41-67%</td>
<td>Equivocal: 41-67%</td>
<td>Equivocal: 41-67%</td>
</tr>
<tr>
<td></td>
<td>Abnormal: &lt; 41%</td>
<td>Abnormal: ≤ 40%</td>
<td>Abnormal: &lt; 41%</td>
</tr>
</tbody>
</table>

Type III, on the other hand, presents with normal C4 and C1-INH levels. Some patients have an associated mutation in the FXII gene, while others have no identified genetic indicators. Type III is very rare (number of cases unknown), and there are no laboratory tests to confirm the diagnosis. Instead, the diagnosis is clinical and supported by recurrent episodes of angioedema with a strong family history of angioedema.

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAE attack prophylaxis</td>
<td>150 mg PO QD</td>
<td>150 mg/day</td>
</tr>
</tbody>
</table>

VI. Product Availability
Capsules: 110 mg, 150 mg

VII. References
5. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03873116, Study to Evaluate the Efficacy and Safety of BCX7353 as an Oral Treatment


<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created pre-emptively</td>
<td>04.14.20</td>
<td>05.20</td>
</tr>
<tr>
<td>Drug is now FDA approved – criteria updated per FDA labeling, amended bypass in 1.b from low C4 to normal C4, updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); references reviewed and updated.</td>
<td>01.12.21</td>
<td>02.21</td>
</tr>
</tbody>
</table>

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to
applicable legal and regulatory requirements relating to provider notification. If there is a
discrepancy between the effective date of this clinical policy and any applicable legal or
regulatory requirement, the requirements of law and regulation shall govern. The Health Plan
retains the right to change, amend or withdraw this clinical policy, and additional clinical
policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is
not intended to dictate to providers how to practice medicine. Providers are expected to exercise
professional medical judgment in providing the most appropriate care, and are solely responsible
for the medical advice and treatment of members. This clinical policy is not intended to
recommend treatment for members. Members should consult with their treating physician in
connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent
judgment and over whom the Health Plan has no control or right of control. Providers are not
agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and
distribution of this clinical policy or any information contained herein are strictly prohibited.
Providers, members and their representatives are bound to the terms and conditions expressed
herein through the terms of their contracts. Where no such contract exists, providers, members
and their representatives agree to be bound by such terms and conditions by providing services to
members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage
provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please
refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.