Original Effective Date: 05/01/2021
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Last P&T Approval/Version: 01/28/2026
Next Review Due By: 07/2026
Policy Number: C21230-A

Orladeyo (berotralstat)

PRODUCTS AFFECTED

Orladeyo (berotralstat)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Hereditary Angioedema (HAE)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. PROPHYLAXIS FOR HEREDITARY ANGIOEDEMA (HAE):
1. Documentation of hereditary angioedema (HAE) diagnosis
   AND
2. Documentation subtype confirmed by ONE of the following [DOCUMENTATION REQUIRED]:
   (a) TYPE 1 OR 2 HAE confirmed by presence of a mutation in the C1-INH gene altering protein

synthesis and/or function
OR
(b) BOTH of the following: (documentation of TWO separate low measurements for each test defined as below the testing laboratory's lower limit of the normal range):
(i) Low serum complement factor 4 (C4) level (< 14 mg/dL) AND
(ii) Low C1 inhibitor (C1-INH) level (C1-INH < 19.9 mg/dL) OR Low C1-INH functional level (functional C1-INH <72%)
AND

3. Prescriber attests concurrent therapies that may exacerbate HAE, have been evaluated and discontinued as appropriate, including: Estrogen-containing medications [e.g., Hormone replacement therapy, contraceptives], ACE-inhibitor (ACEI), Angiotensin II receptor blockers
AND
4. The requested medication is prescribed for routine angioedema prophylaxis in patients with HAE (not for acute use)
AND
5. Documentation of baseline HAE attack severity, duration, and functional abilities, in order to evaluate efficacy of therapy during re-authorization [DOCUMENTATION REQUIRED]
AND
6. Documentation that member has had a trial and failure of or contraindication to Haegarda (C1 esterase inhibitor, human) or Takhzyro (lanadelumab)

CONTINUATION OF THERAPY:

A. PROPHYLAXIS FOR HEREDITARY ANGIOEDEMA (HAE):

1. Subsequent authorizations require re-assessment of treatment regimen/plan, an evaluation of the frequency of HAE attacks and complete clinical review of member's condition to determine if continuation of treatment with requested treatment is medically necessary.
AND
2. Documentation of reduction in frequency of HAE attacks or clinical documentation of functional improvement [DOCUMENTATION REQUIRED]
MOLINA REVIEWER NOTE: The goal of long-term therapy is to decrease or eliminate attacks, and success should be measured by this clinical outcome rather than by laboratory parameters.
AND
3. Member has had an annual evaluation for the continued need for long- term prophylaxis therapy
AND
4. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified immunologist, allergist, geneticist, hematologist, or physician experienced in the treatment of C1-esterase inhibitor deficiency. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

2 years of age and older

QUANTITY:

Adults and pediatrics aged 12 years and older:
150 mg orally once daily
OR
110 mg orally once daily for patients with moderate to severe hepatic impairment, concomitant use with

P-gp or BCRP inhibitors (e.g., cyclosporine), or patients with persistent GI reactions on 150 mg daily

Ages 2 to 12 years: 1 oral pellet packet once daily based on body weight

Weight	Recommended Dosage (oral pellets)
12 kg to less than 24 kg	72 mg once daily
24 kg to less than 32 kg	96 mg once daily
32 kg to less than 40 kg	108 mg once daily
40 kg or greater	132 mg once daily

Maximum Quantity Limits – 1 capsule or packet per day

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Plasma Kallikrein Inhibitors

FDA-APPROVED USES:
Indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 2 years and older
Limitations of Use: Orladeyo should not be used for treatment of acute HAE attacks

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

THERAPIES FOR HEREDITARY ANGIOEDEMA	FDA INDICATION	DOSE	MECHANISM OF ACTION	AGE
Berinert® C1 esterase inhibitor (human)	ACUTE TREATMENT	20 units/kg IV	C1-inhibitor [human]	5 AND OLDER
Ekterly® (sebetralstat)	ACUTE TREATMENT	600 mg PO (may repeat x1)	Plasma kallikrein inhibitor	12 AND OLDER
Firazyr®, Sajazir® Icatibant acetate	ACUTE TREATMENT	30 mg SC	Bradykinin receptor antagonist	18 AND OLDER
Kalbitor® ecallantide	ACUTE TREATMENT	30 mg SC (as three 10 mg/ml injections)	Plasma kallikrein inhibitor	12 AND OLDER
Ruconest® C1-inhibitor (recombinant)	ACUTE TREATMENT	50 units/kg IV (max. 4,200 units)	C1-inhibitor [recombinant]	13 AND OLDER

ANDEMBRY® (garadacimab-gxii)	PROPHYLAXIS	400 mg once, then 200 mg once monthly SC	Activated Factor XII (FXIIa) inhibitor (monoclonal antibody)	12 AND OLDER
Cinryze® C1 esterase inhibitor (human)	PROPHYLAXIS	1,000 units via IV route every 3-4 days	C1-inhibitor [human]	6 AND OLDER
Dawnzera™ (donidalorsen)	PROPHYLAXIS	80 mg every 4 or 8 weeks	Prekallikrein-directed antisense oligonucleotide	12 AND OLDER
Haegarda® C1 esterase inhibitor (human)	PROPHYLAXIS	60 units/kg SC every 3-4 days	C1-inhibitor [human]	6 AND OLDER
Orladeyo® (berotralstat)	PROPHYLAXIS	150 mg PO once daily	Plasma kallikrein inhibitor	2 AND OLDER
Takhzyro® lanadelumab	PROPHYLAXIS	300 mg SC every 2 weeks	Plasma kallikrein inhibitor	2 AND OLDER

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Hereditary angioedema (HAE) is a rare genetic disorder caused by a deficiency in functional C1 inhibitor (C1-INH), resulting in recurrent attacks of localized subcutaneous or mucosal edema most commonly affecting the skin, intestines, upper respiratory tract, and oropharynx. HAE is estimated to affect 1 in 50,000 people in the United States. HAE typically begins in childhood or adolescence and continues throughout the patient's lifetime.

The severity and frequency of edema attacks can vary significantly from person to person. Untreated patients may suffer an attack as often as every few days, while patients undergoing prophylactic therapy may be symptom-free for 10 years or more. In addition to the potential for life- threatening laryngeal edema, patients with HAE can experience painful episodes affecting the GI tract and skin. According to a comprehensive study of U.S. administrative claims data from 274 million covered lives, there are about 10,000 total patients with HAE and 7500 diagnosed and treated HAE patients in the United States.

Orladeyo is the first FDA-approved, orally administered, non-steroidal treatment for HAE prophylaxis. The approval is based on data from the Phase 3 APeX-2 trial (NCT03485911) and the long-term open-label APeX-S trial (NCT03472040) demonstrating that Orladeyo reduced the frequency of HAE attacks. In both studies, the oral, once-daily treatment with Orladeyo was safe and generally well tolerated, with the most common side effect being gastrointestinal (GI) reactions. Orladeyo will compete with the injectable prophylactic therapies for the prevention of HAE attacks, namely Takeda's Cinryze, CSL Behring's Haegarda, and Takeda's Takhzyro.

Utilization of prophylactic therapies for HAE significantly increased following the 2018 approval of Takhzyro, which has quickly become the market leader in the class.

Although Orladeyo does not seem as effective as the other agents in decreasing attack rates, the advantage of oral administration may overcome its less favorable efficacy.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Orladeyo (berotralstat) are considered experimental/investigational and therefore, will

follow Molina's Off- Label policy. Contraindications to Orladeyo (berotralstat) include: No labeled contraindications. Avoid use with P-gp inducers (e.g., rifampin, St. John's Wort). Avoid use in pediatric patients 2 years to less than 12 years of age with moderate or severe hepatic impairment (Child Pugh Class B or C). Avoid use in pediatric patients 2 years to less than 12 years of age with severe renal impairment.

Exclusions/Discontinuation:

Do not use concurrently or in combination with other approved treatments for prophylaxis against HAE attacks (i.e., Haegarda, Cinryze, Takhzyro).

Orladeyo has not been studied in patients with End-Stage Renal Disease (CLCR < 15 mL/min or eGFR < 15 mL/min/1.73 m2 or patients requiring hemodialysis) and therefore is not recommended for use in these patient populations.

OTHER SPECIAL CONSIDERATIONS:

Do not chew or crush Orladeyo oral pellets because this will affect the film coating (taste masking) and result in bitter taste. Administer one packet of oral pellets as follows: Pour the entire contents of one packet directly into the mouth and swallow immediately with nonacidic liquid (e.g., water or milk). OR Sprinkle the entire contents of one packet over approximately one tablespoon (15 mL) of soft, non-acidic food and consume immediately. Food should be at or below room temperature. Examples of soft, non-acidic foods include pudding, mashed potatoes, creamed corn, pureed peas, pureed bananas, and pureed carrots. Acidic foods such as yogurt and applesauce should not be used because they can dissolve the film coating (taste masking) and result in a bitter taste. The film coating (taste masking) remains intact for 10 minutes. If the pellets are not consumed within 10 minutes of sprinkling over food, they should be discarded.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:

Orladeyo CAPS 110MG
Orladeyo CAPS 150MG
Orladeyo Oral Pellets 72mg, 96mg, 108mg, 132mg

REFERENCES

1. Orladeyo (berotralstat) capsules, for oral use [prescribing information]. Durham, NC: BioCryst Pharmaceuticals; December 2025.

2. Lumry WR. Overview of Epidemiology, Pathophysiology, and Disease Progression in Hereditary Angioedema. *Am J Manag Care.* 2013. https://www.ajmc.com/view/ace010_13jun_lumry1_s103to10
3. Zuraw B, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial. *J Allergy Clin Immunol*. 2020. doi:10.1016/j.jaci.2020.10.015
4. Aygören-Pürsün E, et al. P507 BCX7353: An effective and safe oral prophylaxis against attacks of hereditary angioedema. APeX-1 final results. *Ann Allergy Asthma Immunol*. 2017. doi:10.1016/j.anai.2017.09.073
5. Busse, P. J., Christiansen, S. C., Riedl, M. A., Banerji, A., Bernstein, J. A., Castaldo, A. J., … Zuraw, B. L. (2021). US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. The Journal of Allergy and Clinical Immunology: In Practice, 9(1), 132-150.e3. https://doi.org/10.1016/j.jaip.2020.08.046
6. Maurer, M., Magerl, M., Betschel, S., Aberer, W., Ansotegui, I. J., Aygören-Pürsün, E., … Csuka, D. (2022). The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update. Allergy, 2022, 77(7), 1961–1990. https://doi.org/10.1111/all.15214

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Age Restrictions Quantity FDA-Approved Uses Appendix Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms References	Q1 2026
REVISION- Notable revisions: Required Medical Information Duration of Approval Appendix	Q4 2025
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Contraindications/Exclusions/ Discontinuation References	Q3 2025
REVISION- Notable revisions: Required Medical Information Continuation of Therapy FDA-Approved Uses References	Q3 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q3 2023

REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Quantity Contraindications/Exclusions/Discontinuation References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file