Original Effective Date: 05/01/2021
Current Effective Date: 09/15/2024
Last P&T Approval/Version: 7/31/2024
Next Review Due By: 07/2025
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 that all other causes and potentially treatable triggers of HAE attacks (i.e., stress, trauma, infection, etc.) have been identified and optimally managed
AND
4. 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
5. Prescriber attests or the clinical reviewer has found that the requested medication is prescribed for routine angioedema prophylaxis in patients with HAE (not for acute use)
AND
6. Prescriber attests or clinical reviewer has found member is NOT concurrently on, or using in combination with, other approved treatments for prophylaxis against HAE attacks (i.e., Haegarda, Cinryze, Takhzyro)
AND
7. Documentation of baseline HAE attack severity, duration, and functional abilities, in order to evaluate efficacy of therapy during re-authorization [DOCUMENTATION REQUIRED]
AND
8. Prescriber attests a recent review of member's current medication has been completed and there is no concomitant use of P-gp inducers (e.g., rifampin, St. John's wort), and dose adjustment has been made based on labeled recommendations for drug interactions if applicable
AND
9. Documentation that member has had a trial and failure of or contraindication to ONE of the following: Cinryze (C1 esterase inhibitor, human), Haegarda (C1 esterase inhibitor, human), Takhzyro (lanadelumab)

CONTINUATION OF THERAPY:

A. PROPHYLAXIS FOR HEREDITARY ANGIOEDEMA (HAE) TYPE I OR II:

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. Prescriber attests that member has had an annual evaluation for the continued need for long-term prophylaxis therapy
AND
4. Prescriber attests or clinical reviewer has found member is NOT concurrently on, or using in combination with, other approved treatments for prophylaxis against HAE attacks (i.e., Cinryze, Haegarda, Takhzyro)
AND
5. Prescriber attests a recent review of member's current medication has been completed and there is no concomitant use of P-gp inducers (e.g., rifampin, St. John's wort), and dose adjustment has

been made based on labeled recommendations for drug interactions if applicable
AND

6. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:
Initial authorization: 6 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:
12 year of age and older

QUANTITY:
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

Maximum Quantity Limits – 1 capsule1s 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 12 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:
None

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: avoid use with P-gp inducers (e.g., rifampin, St. John's Wort).

OTHER SPECIAL CONSIDERATIONS:

None

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:

Orladeyo CAPS 110MG

Orladeyo CAPS 150MG

REFERENCES

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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.

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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: 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