Original Effective Date: 12/17/2025
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Last P&T Approval/Version: 10/29/2025
Next Review Due By: 07/2026
Policy Number: C29955-A

Ekterly (sebetralstat) MHI

PRODUCTS AFFECTED

Ekterly (sebetralstat)

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. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. TREATMENT OF ACUTE HEREDITARY ANGIOEDEMA TYPE I OR II ATTACKS:
   1. Documentation of Hereditary angioedema (HAE) diagnosis
      AND
   2. Documentation subtype confirmed by ONE of the following [DOCUMENTATION REQUIRED]:

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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):
1. Low serum complement factor 4 (C4) level (< 14mg/dL) AND
2. Low C1 inhibitor (C1-INH) level (C1-INH < 19.9 mg/dL), OR Low C1-INH functional level (functional C1-INH < 72%)

AND

3. The requested medication is prescribed for ACUTE treatment of acute abdominal, facial, or laryngeal HAE attacks associated with HAE (not for routine prophylaxis)
AND
4. Member is NOT concurrently on, or using in combination with, other approved treatments for ACUTE HAE attacks
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. Prescriber provides member's current history of acute attacks and documented evaluation for eligibility for prophylaxis therapy
AND
7. 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
8. FOR ADULT MEMBERS (≥18 YEARS OF AGE): Documentation of trial and failure, or contraindication to icatibant (Firazyr)
AND
9. IF THIS IS A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or serious side effects to a majority (not more than 3) of the preferred formulary/PDL alternatives for the given diagnosis. Submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s).
MOLINA REVIEWER NOTE: For Illinois Marketplace, please see appendix.
AND
10. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Ekterly (sebetralstat) include: avoid use with strong CYP3A4 inhibitors, avoid use with moderate or strong CYP3A4 inducers, and avoid in patients with severe hepatic impairment (Child-Pugh Class C).]

CONTINUATION OF THERAPY:

A. TREATMENT OF ACUTE HEREDITARY ANGIOEDEMA TYPE I OR II ATTACKS:
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 significant improvement in HAE attack severity, duration, or functional abilities [DOCUMENTATION REQUIRED]
AND
3. The member is NOT concurrently on, or using in combination with, other approved treatments for ACUTE HAE attacks
AND

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4. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
5. (a) IF MEMBER IS CONCURRENTLY ON PROPHYLAXIS MEDICATION FOR HAE: Adherence to prophylactic therapy for HAE (with antifibrinolytics, attenuated androgens, or plasma derived C1 inhibitor replacement therapy) OR prescriber attestation that member no longer requires prophylactic therapy
   NOTE: Adherence to prescribed prophylactic therapy for HAE must be confirmed by member's prescription claims. If member is new to Molina and does not have a prescription claims history, Prescriber certifies that the member has been adherent to the prescribed prophylactic therapy.
   OR
   (b) IF MEMBER IS NOT CONCURRENTLY ON A PROPHYLAXIS MEDICATION FOR HAE: Prescriber attests that member has had an annual evaluation for the need for long-term prophylaxis therapy

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:
12 years of age and older

QUANTITY:
Maximum of 4 doses per month (4 or 8 tablets per month)
May authorize up to a sufficient quantity for member to have a cumulative amount on-hand to treat up to 2 acute attacks per month

Maximum Quantity Limits – 1200 mg (4 tablets) in any 24-hour period

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 the treatment of acute attacks of hereditary angioedema (HAE) in adult and pediatric patients aged 12 years and older

COMPENDIAL APPROVED OFF-LABELED USES:
None

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APPENDIX

APPENDIX:

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

State Specific Information

State Marketplace

Illinois (Source: Illinois General Assembly)

"(215 ILCS 134/45.1) Sec. 45.1. Medical exceptions procedures required. (c) An off-formulary exception request shall not be denied if: (1) the formulary prescription drug is contraindicated; (2) the patient has tried the formulary prescription drug while under the patient's current or previous health insurance or health benefit plan and the prescribing provider submits evidence of failure or intolerance; or (3) the patient is stable on a prescription drug selected by his or her health care provider for the medical condition under consideration while on a current or previous health insurance or health benefit plan. (d) Upon the granting of an exception request, the insurer, health plan, utilization review organization, or other entity shall authorize the coverage for the drug prescribed by the enrollee's treating health care provider, to the extent the prescribed drug is a covered drug under the policy or contract up to the quantity covered. (e) Any approval of a medical exception request made pursuant to this Section shall be honored for 12 months following the date of the approval or until renewal of the plan."

Appendix 1: Dosage Modifications:

Dosage Modification for Concomitant use with CYP3A4 Inhibitors	
Strong CYP3A4 Inhibitors	AVOID
Moderate CYP3A4 Inhibitors	Reduce dose to 300 mg (one tablet) at earliest recognition of an acute HAE attack. A second 300 mg (on tablet) may be taken at least 3 hours after the first dose if response is inadequate or symptoms worsen or recur.
Weak CYP3A4	No dosage modification required

Dosage Modification for Concomitant use with CYP3A4 Inducers	
Strong or Moderate CYP3A4 Inducers	AVOID
Weak CYP3A4 Inducers	No dosage modification required

Dosage Modification for Hepatic Impairment	
Severe Hepatic Impairment (Child-Pugh Class C)	AVOID
Moderate Hepatic Impairment (Child-Pugh Class B)	Reduce dose to 300 mg (one tablet) at earliest recognition of an acute HAE attack. A second 300 mg (on tablet) may be taken at least 3 hours after the first dose if response is inadequate or symptoms worsen or recur.
Mild Hepatic Impairment (Child-Pugh Class A)	No dosage modification required

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Appendix 2:

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	12 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)

A rare genetic disorder of recurrent attacks of localized subcutaneous or mucosal swelling that affects 1 in 10,000 to 1 in 50,000 individuals in the United States. Attack frequency varies from a few days to decades between attacks and severity ranges from mild to more severe laryngeal edema causing airway obstruction and fatal asphyxiation. Formal diagnosis is often significantly delayed following onset of

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symptoms and misdiagnosis or medical mismanagement is not uncommon. The two most common forms of HAE (Types I and II) may be managed with prophylaxis or acute treatment depending on attack frequency, severity, and drug tolerability.
HAE type 1 and HAE type 2 are the most common forms of HAE. HAE type 1 involves a deficiency in C1 inhibitor and HAE type 2 involves a dysfunction in the C1 inhibitor (C1-INH). Both result in the overproduction of bradykinin. This results in an increased vascular permeability and subsequent angioedema attacks. Attacks can be abdominal, peripheral (impairing hand and foot function) or effecting the airways with risk for asphyxiation. Attacks should be treated as early as possible.
There is also HAE with normal C1-INH, previously called type 3. The 2021 revision of the international WAO/EAACI guideline (ref. 10) for the management of hereditary angioedema calls for HAE with normal C1-INH to be reevaluated and omits this condition from its management recommendations. A 2025 international consensus paper (ref. 11) discusses HAE-nC1IHN (normal C1IHN function). Six different genetic mutations have been linked to HAE-nC1IHN. While the treatment strategies used for HAE-nC1INH are similar to those of HAE type 1 and 2, the available information is from case reports and small case series and response to treatment may differ across subtypes.

Sebetralstat is an oral plasma kallikren inhibitor. Plasma kallikren is a protease that cleave kininogen, releasing bradykinin. Inhibition of that cleavage results in a reduction in the production of the bradykinin.

The safety and efficacy of oral sebetralstat for on-demand treatment for hereditary angioedema attacks was studied in the KONFIDENT trial [NCT05259917]. This was a phase 3, double blind, three-way crossover trial which included patients (n=136) of at least 12 years of age with type 1 or type 2 hereditary angioedema. Key inclusion criteria includes a confirmed diagnosis of HAE type I or II, age of 12 years or older, and, for patients on a prophylactic therapy, the dose (with the exception of danazol), the regimen and dose had to be stable for at least 3 months. For patients on danazol, the dose was required to be stable for at least 6 months. Patients were also required to have had at least 2 documented HAE attacks within 3 months prior to the study screening or randomization. Key exclusion requirements included:

- Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1-inhibitor deficiency, HAE with normal C1-INH (previously known as HAE type III), idiopathic angioedema, or angioedema associated with urticaria.
- A clinically significant history of poor response to bradykinin receptor 2 (BR2) blocker, C1-INH therapy or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the Investigator.
- Use of angiotensin-converting enzyme (ACE) inhibitors after the Screening Visit or within 7 days prior to randomization.

Patients were randomly assigned to sebetralstat 300 mg, sebetralstat 600 mg, or placebo for an angioedema attack. Symptom relief was assessment using a time-to-event analysis. Both doses of sebetralstat provided relief faster than placebo ($p<0.001$ and $p=0.001$, respectively). The time to reduction in attack severity was also statistically faster than placebo ($p=0.004$ and $p=0.003$). The median time to reduction in attach severity was 9.27 hours for 300 mg, 7.75 hours for 600 mg and more than 12 hours for placebo. Both sebetralstat and placebo had similar safety profiles. No serious adverse events related to sebetralstat were reported in the trial. The most common adverse reaction reported was headache.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Ekterly (sebetralstat) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Ekterly (sebetralstat) include: avoid use with strong CYP3A4 inhibitors, avoid use with moderate or strong CYP3A4 inducers, and avoid in patients with severe hepatic impairment (Child-Pugh Class C).

OTHER SPECIAL CONSIDERATIONS:
Sebetralstat is taken orally at the earliest recongition of an HAE attack. A second dose (2- 300 mg tablets) may be take 3 hours after the first dose if response is inadequate or if symptoms worsen or recur. For

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patients taking a moderate CYP3A4 inhibitor, dose is reduced to one 300 mg tablet for both initital and second dose, if required. For members with moderate hepatic impairment (Child-Pugh Class B), the dose is reduced to one 300 mg tablet for both initital and second dose, if required.

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:
Ekterly TABS 300MG

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SUMMARY OF REVIEW/REVISIONS	DATE
NEW CRITERIA CREATION	Q4 2025

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