Kalbitor (ecallantide)
Policy Number: C6772-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
40238	6/17/2020	6/17/2021
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
J1290-injection, ecallantide, 1mg	RxPA	Q3 2020 20200722C6772-A

PRODUCTS AFFECTED:
Kalbitor (ecallantide)

DRUG CLASS:
Plasma Kallikrein Inhibitors

ROUTE OF ADMINISTRATION:
Subcutaneous

PLACE OF SERVICE:
Specialty Pharmacy or Buy and Bill
The recommendation is that medications in this policy will be for pharmacy benefit coverage and Self- administered
If required- can be administered in a place of service that is a non-hospital facility-based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center)

AVAILABLE DOSAGE FORMS:
Kalbitor SOLN 10MG/ML

FDA-APPROVED USES:
Treatment of acute attacks of hereditary angioedema in members 12 years and older

COMPENDIAL APPROVED OFF-LABELED USES:
Hereditary angioedema with normal C1 inhibitor levels

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS:
acute attacks of hereditary angioedema

REQUIRED MEDICAL INFORMATION:
A. TREATMENT OF ACUTE HEREDIATRY ANGIOEDEMA ATTACKS:

1. Documentation of HAE diagnosis and subtype confirmed by ONE of the following:
   (a) TYPE 1 OR 2 HAE; Presence of a mutation in the C1-INH gene altering protein synthesis and/or function
   OR
   (b) BOTH of the following: (documentation of TWO (2) separate low measurements foreach 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

2. Prescribed for ACUTE treatment of acute abdominal, facial, or laryngeal HAEattacks associated with HAE (not for routine prophylaxis) AND
3. Documentation of baseline record of the following aspects of HAE attacks: Severity, Duration and functional abilities in order to evaluate efficacy during re-authorization
4. All other causes and potentially treatable triggers of HAE attacks (i.e. stress,trauma, infection, etc.) have been identified and optimally managed
AND
5. Concurrent therapies that may exacerbate HAE, have been evaluated and has been discontinued as appropriate, including: Estrogen-containing medications [e.g. hormone replacement therapy, contraceptives], ACE-inhibitor (ACEI), Angiotensin II receptor blockers
AND
6. Member is NOT concurrently on, or using in combination with, other approved treatments for ACUTE HAE attacks (e.g. Firazyr, Ruconest, and Berinert)
AND
7. (a) FOR ADULT MEMBERS >18 YEARS OF AGE): Documentation of trial, failure or contraindication to Firazyr (icatibant)
OR
(b) FOR CHILDREN AGES 12-18 YEARS: Documentation of trial, failure or contraindication to Berinert (C1 esterase inhibitor, human)

B. HAE WITH NORMAL C1 INHIBITOR LEVELS (PREVIOUSLY CALLED TYPE III HAE):

1. Documented diagnosis HAE with normal C1 inhibitor levels as evidenced by normal C4 level and normal C1-INH levels AND any of the following: (i) Episodic angioedema affecting characteristic organs, without urticaria, (ii) a documented family history of angioedema, (iii) presence of a FXII (or possibly an angiopoietin-1 or plasminogen mutation) associated with the disease
AND
2. IF THIS IS A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or intolerance to a majority (not more than 3) of the preferred/formulary alternatives for the given diagnosis. If yes, please submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s)
AND
3. (a) FOR ADULT MEMBERS >18 YEARS OF AGE): Documentation of trial, failure or contraindication to Firazyr (icatibant)
OR
(b) FOR CHILDREN AGES 5-17 YEARS: Documentation of trial, failure or contraindication to Berinert (C1 esterase inhibitor, human)
AND
4. Member is NOT concurrently on, or using in combination with, other approved treatments for ACUTE HAE attacks (e.g. Firazyr®, Ruconest®, and Berinert®)

DURATION OF APPROVAL:
Initial authorization: 6 months, Continuation of therapy: 12 months

QUANTITY:
30 mg (3 mL) administered subcutaneously in three 10 mg (1 mL) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24-hour period. Must be administered by

a health care provider. 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.

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified immunologist, allergist, hematologist, or physician experienced in the treatment of C1-esterase inhibitor deficiency. Submit consultation notes if applicable.

AGE RESTRICTIONS:
12 years of age or older

CONTINUATION OF THERAPY:
A. TREATMENT OF ACUTE HEREDIATRY ANGIOEDEMA ATTACKS:

1. Subsequent authorizations require re-assessment 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. Submit all relevant clinical notes, chart notes, and consultation notes (if applicable) for review at least once every 6 months
   AND
2. Documentation of significant improvement in the following aspects of HAE attacks have been achieved: Severity, Duration or Clinical documentation of functional improvement
   AND
3. (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) 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 certify that the member has been adherent to the prescribed prophylactic therapy.
   OR
   (b) IF MEMBER IS NOT CONCURRENTLY ON A PROPHYLAXIS MEDICATION OF HAE: Prescriber attests that member has had an annual evaluation for the need for long-term prophylaxis therapy

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Kalbitor (ecallantide) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications include: History of life-threatening immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations

OTHER SPECIAL CONSIDERATIONS:

THERAPIES FOR HEREDITARY ANGIOEDEMA

	FDA INDICATION	DOSE	MECHANISM OF ACTION	AGE INDICATIONS
Berinert® C1 esterase inhibitor (human)	ACUTE TREATMENT	20 units/kg IV	C1-inhibitor [human]	5 AND OLDER
Ruconest® C1-inhibitor (recombinant)	ACUTE TREATMENT	50 units/kg IV (max. 4,200 units)	C1-inhibitor [recombinant]	13 AND OLDER
Kalbitor® ecallantide	ACUTE TREATMENT	30 mg SC (as three 10 mg/ml injections)	Plasma kallikrein inhibitor	12 AND OLDER

Firazyr® Icatibant acetate	ACUTE TREATMENT	30 mg SC	Bradykinin receptor antagonist	18 AND OLDER
Cinryze® C1 esterase inhibitor (human)	PROPHYLAXIS	1,000 units via IV route every 3-4 days	C1-inhibitor [human]	6 AND OLDER
Haegarda® C1 esterase inhibitor (human)	PROPHYLAXIS	60 units/kg SC every 3-4 days	C1-inhibitor [human]	12 AND OLDER
Takhzyro® lanadelumab	PROPHYLAXIS	300 mg SC every 2 weeks	Plasma kallikrein inhibitor	12 AND OLDER

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 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-1/2 is a rare autosomal dominant condition affecting an estimated 1 in 50,000 individuals, although this may vary in different regions. HAE-1/2 is caused by one of more than 450 different mutations in the SERPING1 gene, which codes for C1-INH [40]. In approximately 20–25% of patients, a de novo mutation of SERPING1 is responsible for the disease. C1-INH is a serine protease inhibitor (SERPIN) and the major inhibitor of several complement proteases (C1r, C1s, and mannose-binding lectin–associated serine protease [MASP] 1 and 2) and contact-system proteases
(plasma kallikrein and coagulation factor XIIa) as well as a relatively minor inhibitor of the fibrinolytic protease plasmin.
The primary mediator of swelling in HAE-1/2 is bradykinin [28]. Bradykinin is a low molecular weight nonapeptide, which is generated when active plasma kallikrein cleaves high molecular weight kininogen (HMWK). Bradykinin is rapidly metabolized by endogenous metalloproteases including angiotensin-converting enzyme (ACE). Plasma kallikrein is activated from its inactive zymogen prekallikrein
by the protease factor XII, which can easily autoactivate upon contact with negatively-charged surfaces. Both, plasma kallikrein and factor XII are inhibited by C1-INH. Increased vascular permeability induced by the liberation of bradykinin in angioedema is primarily mediated through the bradykinin B2 receptor.

HAE with normal C1 inhibitor

HAE with normal C1-INH (HAE nC1-INH) is a very rare disease. Its clinical appearance largely resembles that of HAE-1/2. In a subgroup of patients, HAE nC1-INH is associated with mutations of the factor XII (FXII-HAE) gene. Recently, two new mutations in - (ANGPT1) and plasminogen (PLG) were reported in HAE nC1-INH. However, in most patients with HAE nC1-INH, no
gene mutation can be found, and the pathogenesis remains to be characterized in detail. However, there is clinical evidence that bradykinin may play a major role in some types of HAE nC1-INH, primarily in patients with a FXII-mutation [52–54]. Although HAE nC1-INH shares some clinical

features and, possibly, therapeutic options with HAE-1/2, this guideline is for HAE-1/2.

C1-Inh Deficiency	Inherited	HAE-1 hereditary angioedema due to C1-Inhibitor deficiency, HAE-2 hereditary angioedema due to C1-Inhibitor dysfunction
	Acquired	AAE-C1-INH acquired angioedema due to C1-Inhibitor deficiency
C1 Inh- Normal	Inherited	HAE nC1-INH hereditary angioedema with normal C1-Inhibitor levels, either due to a mutation in FXII, ANGPTI, PLG or unknown (HAE-FXII, HAE-ANGPTI, HAE-PLG, HAE-UNK),
	Acquired	ACEI-AE angiotensin converting enzyme inhibitor-induced angioedema

APPENDIX:

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, member 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.

REFERENCES:

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2. Craig T, Pursun EA, Bork K, et al. WAO guideline for the management ofhereditary angioedema. WAO Journal. 2012;5:182-199.
3. Agostoni, Angelo, et al. "Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond." Journalof Allergy and Clinical Immunology 114.3 (2004): S51- S131.
4. Bork K, Bernstein JA, Machnig T, Craig TJ. Efficacy of different medical therapies for the treatment of acute laryngeal attacks of hereditary angioedema due to C1-esteraseinhibitor deficiency. J Emerg Med. 2016 Apr;50(4):567-580.
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6. Bork K. Hereditary angioedema with normal C1 inhibitor activity including hereditary angioedema with coagulation factor XII gene mutations. Immunol Allergy Clin North Am 2006;26:709-24, III.