Haegarda (C1 Esterase Inhibitor Subcutaneous [human]) Policy Number: C12157-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DUE BY OR BEFORE
12/1/2017	1/21/2021	1/26/2022
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
J0599-Injection, C1 esterase inhibitor (human), (haegarda), 10units	RxPA	Q1 2021 20210127C12157-A

PRODUCTS AFFECTED:
Haegarda (C1 Esterase inhibitor subcutaneous, human)

DRUG CLASS:
C1 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:
Haegarda SOLR single-dose vials containing 2000 or 3000 International Units (IU)

FDA-APPROVED USES:
Haegarda is indicated for the routine prophylaxis of angioedema attacks in patients 6 years of age and older

COMPENDIAL APPROVED OFF-LABELED USES:
None

COVERAGE CRITERIA: INITIAL

AUTHORIZATION DIAGNOSIS:
hereditary angioedema

REQUIRED MEDICAL INFORMATION:
A. PROPHYLAXIS FOR HEREDITARY ANGIOEDEMA (HAE):

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 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%)

2. All other causes and potentially treatable triggers of HAE attacks (i.e. stress, trauma, infection, etc.) have been identified and optimally managed
   AND
3. 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
4. Member is NOT concurrently on, or using in combination with, other approved treatments for prophylaxis against HAE attacks (i.e. Cinryze,Takhzyro)
   AND
5. Documentation of baseline record of the following aspects of HAE attacks: Severity, Duration and functional abilities, in order to evaluate efficacy during re-authorization
   AND
6. FOR ADULT PATIENTS ≥18 YEARS OF AGE): Documentation of trial, failure or contraindication to Takhzyro (lanidalimab)
   OR
7. FOR CHILDREN AGES 6-17YEARS: Documentation of trial, failure, or contraindication to Cinryze (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. Member is NOT concurrently on, or using in combination with, other approved treatments for PROPHYLAXIS OF HAE attacks [e.g. Cinryze, Takhzyro (lanidalimab)]
   AND
3. Documentation of patient weight taken within the previous 30 days
   AND
4. Documentation of baseline record of the following aspects of HAE attacks: Severity, Duration and functional abilities, in order to evaluate efficacy during re-authorization
   AND
5. FOR ADULT PATIENTS >18 YEARS OF AGE): Documentation of trial, failure or contraindication to Takhzyro (lanidalimab)
   OR
   FOR CHILDREN AGES 12-17 YEARS: Documentation of trial, failure, or contraindication to Cinryze (C1 esterase inhibitor, human)

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

QUANTITY:
maximum of 2 doses per week and 8 doses per 28 days
Doses less than 2,000 IU, must use (1) 2,000 IU vial,
Doses greater than 2,000IU but less than 3,000IU, must use (1) 3,000IU vial,
Doses greater than 3,000IU but less than 4,000IU, must use (2) 2,000IU vials,
Doses greater than 4,000IU but less than 5,000IU must use (1) 2,000IU vial and (1) 3,000IU vial,
Doses greater than 5,000 but less than 6,000IU can use either (3) 2,000IU vial OR (2) 3,000IU vial,
Doses greater than 6,00IU but less than 8,000IU must use (2) 3,000IU vials AND

(1) 2,000IU vial, Doses greater than 8,000IU but less than 9,000IU must use (3) 3,000IU vials, Doses greater than 9,000IU, must utilize vial optimization

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:
6 years of age or older

CONTINUATION OF THERAPY:
A. ALL INDICATIONS

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 12 months.
   AND
2. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)
   AND
3. Documentation of significant improvement in the following aspects of HAE attacks have been achieved: Severity, Duration or Clinical documentation of functional improvement
   AND
4. Prescriber attests that member has had an annual evaluation for the continued need for long- term prophylaxis therapy

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Haegarda (C1 esterase inhibitor, human) 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

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]	6 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:

Molina Healthcare, Inc. covers injectable/infused treatment in a hospital outpatient setting or at a hospital-affiliated infusion suite* when the level of care is determined to be medically necessary. Considerations used to determine if an alternative level of care is not suitable may include the following findings:

1. The patient is clinically unstable based on documented medical history and susceptible to complication with drug administration (e.g., cardiopulmonary orrenal dysfunction, risk for fluid overload)
2. The requested medication is administered as part of a chemotherapy regimen(e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer or with dialysis
3. The patient exhibits physical or cognitive impairment and a capable caregiver isnot available to assist with safe administration of prescribed medication in thehome
4. It is the patient's first dose of the medication or it is being re-initiated after at least 12 months*
5. The patient has experienced adverse events with past administration of the drug and cannot be managed by premedication or resources available at an non-hospital facility based location (NHFBL)
6. Documented history of difficulty establishing and maintaining patent vascularaccess, or is not a candidate for a mode of long-term vascular access during the duration of prescribed treatment

Note: a hospital outpatient setting, or a hospital-affiliated infusion suite is expected to have

immediate access to specific services of a medical center/hospital setting, including having emergency resuscitation equipment and personnel (ACLS protocol), emergency services, and inpatient admission or intensive care, if necessary

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.

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