Utilization Review Policy 128

POLICY: Hereditary Angioedema – Icatibant Utilization Management Medical Policy

- Firazyr® (icatibant subcutaneous injection – Takeda, generic)
- Sajazir™ (icatibant subcutaneous injection – Cycle)

EFFECTIVE DATE: 1/1/2020
LAST REVISION DATE: 10/29/2025

COVERAGE CRITERIA FOR: All UCare Plans

OVERVIEW

Icatibant is a synthetic decapeptide that is indicated for the **treatment of acute hereditary angioedema (HAE) attacks** in adults ≥ 18 years of age.[1]

Guidelines

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1 esterase inhibitor (C1-INH) antigenic level, and C1-INH functional level.[2] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The goal of acute therapy is to minimize morbidity and prevent mortality from an ongoing HAE attack. Patients must have ready access to effective on-demand medication to administer at the onset of an HAE attack. All HAE attacks are eligible for treatment, irrespective of the location of swelling or severity of the attack. First-line treatments include plasma-derived C1-INH, Ruconest® (C1-INH [recombinant] intravenous [IV] infusion), Kalbitor® (ecallantide subcutaneous injection), and icatibant.

The guidelines note that HAE with normal C1-INH (HAE-nC1INH) is challenging to diagnose due to the lack of validated biochemical test.[2] Genetic testing could be helpful in confirming diagnosis. The most common mutation linked to HAE-nC1INH is in the F12 gene. These guidelines note the following criteria for diagnosis of HAE-nC1INH: a history of recurrent angioedema without hives and no concomitant use of medication-related angioedema; documented normal or near normal C4, C1-INH antigen, and C1-INH function; and either a mutation associated with the disease or a positive family history of recurrent angioedema and documented lack of efficacy of high-dose antihistamine therapy (i.e., cetirizine at 40 mg/day or the equivalent) for at least 1 month or an interval expected to be associated with three or more angioedema attacks, whichever is longer. Supportive evidence includes a history of rapid and durable response to a bradykinin-targeted medication and predominant documented visible angioedema or in patients with abdominal symptoms, evidence of bowel wall edema documented by imaging. With regards to on-demand treatment of HAE-nC1INH, the guidelines note the lack of randomized controlled studies. However, it notes that there are numerous open-label reports with successful responses to on-demand treatments used for HAE type I/II. There are no data on short-term prophylaxis for HAE-nC1INH. Use of C1INH replacement for long-term prophylaxis is noted to be complex and controversial.

In guidelines from the World Allergy Organization/European Academy of Allergy and Clinical Immunology (2021), it is recommended that all attacks be treated with either IV C1-INH, Kalbitor, or icatibant (evidence level A for all).[3] Regarding IV C1-INH, it is noted that Berinert® (C1 esterase inhibitor [human] IV infusion) and Cinryze® (C1 esterase inhibitor [human] IV infusion) are both plasma-derived products available for this use, although indications vary globally. It is essential that patients have on-

demand medication to treat all attacks; thus, the guidelines recommend that patients have and carry medication for treatment of at least two attacks.

An international consensus paper was published on the diagnosis, pathophysiology, and treatment of HAE-nl-C1INH.[4] The paper notes there is a paucity of high-level evidence in HAE-nC1INH and that all recommendations are based on expert opinion. Mutations in six different genes have been linked to HAE-nC1INH; however, the paper also specifies that many patients still lack an identified pathogenic variant for HAE-nC1INH. The six known gene variants are the following: the genes for coagulation factor XII (*F12 or FXII*), plasminogen (*PLG*), angiopoietin-1 (*ANGPT1*), kininogen-1 (*KNG1*), myoferlin (*MYOF*), and heparan sulfate glucosamine 3-O-sulfotransferase-6 (*HS3OST6*). Two more additional genes have been identified in the past year that have been linked to HAE-nC1INH in families that also experienced hives, the gene for carboxypeptidase N (*CPN*) and disabled homolog 2 interacting protein (*DAB2IP*). HAE-FXII and HAE-PLG appear to be bradykinin-mediated; the underlying mechanism of the other types have not been clearly identified. HAE-nC1INH patients have either a family history of recurrent angioedema or a genetic pathogenic variant in one of the known genes. Patients with HAE-unknown (HAE-UNK) have the phenotype indicative of HAE-nC1INH (recurrent angioedema that is not mast cell-mediated, normal C1INH function, and a positive family history of angioedema), but do not have an identified pathogenic variant. The diagnosis is based on exclusion of other causes such as HAE type I/II, mast-cell mediated angioedema, and medication-associated angioedema. Compared to mast-cell mediated angioedema, HAE-nC1INH attacks tend to progress slower, last longer, and are more likely to involve the abdomen or require intubation. Patients with HAE-nC1INH show no response to high-dose H1 antihistamines, corticosteroids, epinephrine, leukotriene receptor antagonists, or Xolair® (omalizumab for subcutaneous use). For management of HAE-nC1INH attacks, treatment with a plasma-derived C1 INH concentrate, bradykinin B2 receptor antagonist (icatibant), or plasma kallikrein inhibitor (Kalbitor) are noted to be generally effective. The consensus paper also notes there are limitations to diagnosing HAE-nC1INH on clinical signs and symptoms alone due to much variability even with a family with the same pathogenic variant. The paper notes that inclusion of family history as a required criterion for HAE might be problematic since this could be unreliable. The presence of a family history of angioedema may be considered strongly supportive of an HAE diagnosis, but cannot be an absolute requirement for diagnosis. There are very limited data on the use of short-term or long-term prophylaxis for HAE-nC1INH. Long-term prophylaxis with antifibrinolytics, such as tranexamic acid, appear to benefit some subtypes of HAE-nC1INH (e.g., HAE-PLG). Data on Takhzyro (lanadelumab-flyo injection) use for prophylaxis are also very limited; a Phase III trial failed to demonstrate a difference, compared with placebo, in reducing the number of HAE-nC1INH attacks.[5]

Table 1. Laboratory Diagnosis of Hereditary Angioedema.[2-4]

Laboratory Test	HAE Type I	HAE Type II	HAE - nC1INH (Formerly HAE Type III)
C4 Level	Low	Low	Normal
C1-INH protein/antigenic level	Low	Normal or high	Normal
C1-INH functional level	Low	Low	Normal
Genetic mutations	Mutation in SERPING1 gene	Mutation in SERPING1 gene	Mutations in other genes (e.g., F12, PLG)

HAE – Hereditary angioedema; HAE-nC1INH – Hereditary angioedema with normal C1 inhibitor; F12 – Gene for factor XII; PLG – Gene for plasminogen.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of icatibant. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing

documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). Because of the specialized skills required for evaluation and diagnosis of patients treated with icatibant, approval requires icatibant to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. A patient who has previously met initial therapy criteria for icatibant for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., patient who has treated previous HAE attacks with icatibant). If past criteria have not been met under the Coverage Review Department and the patient has treated previous HAE attacks with icatibant, initial therapy criteria must be met.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of icatibant is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks**. Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial therapy. Approve if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
   - **B)** Patient who has treated previous HAE attacks with icatibant. Approve if the patient meets ALL of the following (i, ii, and iii):
     Note: If the patient is currently receiving the requested therapy but has not previously received approval of icatibant for this indication through the Coverage Review Department, review under criteria for Initial Therapy.
     - **i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
     - **ii.** According to the prescriber, the patient has had a favorable clinical response with icatibant treatment; AND
       Note: Examples of a favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

Dosing. Approve up to 30 mg per injection, administered subcutaneously no more frequently than three times daily.

Other Uses with Supportive Evidence

---

2. Hereditary Angioedema (HAE) With Normal C1 Inhibitor (C1-INH) – Treatment of Acute Attacks.

Note: This is also known as HAE type III.

Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient meets BOTH of the following (a and b):

a) Patient has normal levels of C1-INH (protein level and/or functional activity), as defined by the laboratory reference values **[documentation required]**; AND

b) Patient has normal serum C4 levels, as defined by the laboratory reference values **[documentation required]**; AND

ii. According to the prescriber, the recurrent angioedema attacks are not responsive to high-dose oral H_1 antihistamine therapy; AND

Note: High dose oral H_1 antihistamine therapy is the highest dose tolerated by the patient and can be up to four times the FDA-approved dose.

iii. Patient meets ONE of the following (a or b):

a) Patient has a confirmed pathogenic variant in ONE of the following: factor XII (*F12*), plasminogen (*PLG*), angiopoietin-1 (*ANGPT1*), kininogen-1 (*KNG1*), myoferlin (*MYOF*), and heparan sulfate glucosamine 3-*O*-sulfotransferase-6 (*HS3OST6)* **[documentation required]**; OR

b) Patient meets BOTH of the following (1 and 2):

(1) A pathogenic variant has not been identified [**documentation required]**; AND

(2) Patient meets ONE of the following (a or b):

a. Patient has a known family history of HAE with normal C1 inhibitor; OR

b. Patient has a family history of recurrent angioedema without hives; AND

iv. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders; OR

B) Patient has treated previous HAE attacks with icatibant. Approve if the patient meets ALL of the following (i, ii, and iii):

Note: If the patient is currently receiving the requested therapy but has not previously received approval of icatibant for this indication through the Coverage Review Department, review under criteria for Initial Therapy.

i. Patient has a diagnosis of HAE with normal C1-INH **[documentation required]**; AND

ii. According to the prescriber, the patient has had a favorable clinical response with icatibant treatment; AND

Note: Examples of a favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.

iii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

Dosing. Approve up to 30 mg per injection, administered subcutaneously no more frequently than three times daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of icatibant is not recommended in the following circumstances:

1. **Hereditary Angioedema (HAE) Prophylaxis**. Data are not available and icatibant is not indicated for prophylaxis of HAE attacks.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Firazyr® subcutaneous injection [prescribing information]. Lexington, MA: Takeda; October 2021.
2. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
3. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.
4. Zuraw BL, Bork K, Bouillet L, et al. Hereditary angioedema with normal C1 inhibitor: an updated international consensus paper on diagnosis, pathophysiology, and treatment. *Clin Rev Allergy Immunol.* 2025;68:24.
5. Riedl MA, Staubach P, Farkas H, et al. Lanadelumab for prevention of attacks of non-histaminergic normal C1 inhibitor angioedema: results from the randomized, double-blind CASPIAN study and CASPIAN open-label extension. *Front. Immunol*. 2025 May 21;16:1502325.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	09/21/2022
Annual Revision	It was added to the Policy Statement that a person who has previously met initial therapy criteria for icatibant for the requested indication under the Coverage Review Department and has treated previous HAE attacks with icatibant, is only required to meet the continuation of therapy criteria (i.e., patient has treated previous HAE attacks with icatibant). If past criteria have not been met under the Coverage Review Department and the patient has treated previous HAE attacks with icatibant, initial criteria must be met. In addition, the following changes were made: **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient who has treated previous HAE attacks with icatibant", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through a different entity .	09/20/2023
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024
Annual Revision	No criteria changes.	10/09/2024
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/15/2025
Annual Revision	**Hereditary Angioedema (HAE) With Normal C1 Inhibitor (C1-INH) – Treatment of Acute Attacks**. Added new approval condition and requirements under "Other Uses with Supportive Evidence".	10/29/2025