Drug Coverage Policy

Effective Date.....01/01/2026
Coverage Policy Number.....IP0335
Policy Title.....Icatibant

Hereditary Angioedema - Icatibant

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

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

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]

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.

Coverage Policy

POLICY STATEMENT

Prior Authorization is required for 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. All documentation must include patient-specific identifying information.

Icatibant products (Firazyr [brand, generic] or Sajazir) are considered medically necessary when ONE of the following is met (1 or 2):

FDA-Approved Indication

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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 ALL of the following (i, ii, and iii):
     - **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; AND
     - **iii.** Preferred product criteria is met, for the product(s) as listed in the below table(s); OR
   - **B)** Patient who has treated previous HAE attacks with icatibant. Approve if the patient meets ALL of the following (i, ii, iii, and iv):
     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; AND
     - **iv.** Preferred product criteria is met, for the product(s) as listed in the below table(s).

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

Other Uses with Supportive Evidence

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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, iv, and v):
- **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; AND
- **v.** Preferred product criteria is met, for the product(s) as listed in the below table(s); OR

B) Patient has treated previous HAE attacks with icatibant. Approve if the patient meets ALL of the following (i, ii, iii, and iv):
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; AND
- **iv.** Preferred product criteria is met, for the product(s) as listed in the below table(s)

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

Employer Plans:

Non- Preferred Product	Criteria
Firazyr	The patient has tried generic **icatibant** (the bioequivalent generic product) AND cannot continue to use due to a formulation difference in the inactive ingredient(s) [e.g., differences in stabilizing agent, buffering agent, and/or surfactant] between the brand and the bioequivalent generic product which, per the prescriber, would result

Non- Preferred Product	Criteria
	in a significant allergy or serious adverse reaction **[documentation required].**
Sajazir	The patient has tried generic **icatibant** (the bioequivalent generic product) AND cannot continue to use due to a formulation difference in the inactive ingredient(s) [e.g., differences in stabilizing agent, buffering agent, and/or surfactant] between the brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction **[documentation required].**

Individual and Family Plans:

Non-Preferred Product	Criteria
Firazyr	The patient has tried generic **icatibant or Sajazir** (the bioequivalent generic product) AND cannot continue to use due to a formulation difference in the inactive ingredient(s) [e.g., differences in stabilizing agent, buffering agent, and/or surfactant] between the brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction **[documentation required].**

Conditions Not Covered

Icatibant products (Firazyr [brand, generic] or Sajazir) for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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

Coding Information

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.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J1744	Injection, icatibant, 1 mg

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.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Updated** review date, disclaimer, refreshed background and references, and addition of change history.	1/15/2025
Annual Revision	**Updated** documentation requirements throughout the policy where required. **For Employer Plans: Updated** Sajazir from Preferred to a Non-Preferred product and now requires documentation that the "patient has tried generic icatibant (the bioequivalent generic product) AND cannot continue to use due to a formulation difference in the inactive ingredient(s) [e.g., differences in stabilizing agent, buffering agent, and/or surfactant] between the brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction". **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency - Treatment of Acute Attacks** **Added** "Due to C1 Inhibitor (C1-INH) Deficiency" to indication name **Added** "Patient has HAE type I or type II as confirmed by the following diagnostic criteria" and also **added** "Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement." **Removed** "Confirmed pathogenic variant in the *SERPING1, F12, ANGPT1*, *PLG* or *KNG1* gene" **Removed** "Icatibant will not be concomitantly administered with other FDA-approved treatments	01/01/2026

	for acute HAE attacks (for example Berinert, Cinryze, Kalbitor, or Ruconest)" **Added** "a physician who specializes in the treatment of HAE or related disorders" to specialist requirement. **Added** criteria for "Patient who has treated previous acute HAE attacks with icatibant" **Updated** preferred product criteria to include the following examples of formulation differences in the inactive ingredient(s) "[e.g., differences in stabilizing agent, buffering agent, and/or surfactant] between the brand and the bioequivalent generic product". **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". **Conditions Not Covered** **Removed** C1-Inhibitor normal (levels and function) episodes of angioedema not related to a documented pathogenic variant in the *F12, ANGPT1, PLG,* or *KNG1* gene.	

The policy effective date is in force until updated or retired.