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Hereditary Angioedema (HAE) Therapy

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Related Coverage Resources

[Genetic Testing for Hereditary and Multifactorial Conditions](#)

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. 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.

Coverage Policy

Treatment of hereditary angioedema (HAE) includes the following products:

- **C1 Esterase Inhibitor [Human] (Haegarda®)**
- **ecallantide (Kalbitor®)**
- **icatibant (Firazyr®)**
- **icatibant (Sajazir™)**
- **lanadelumab-flyo (Takhzyro®)**

C1 Esterase Inhibitors [Human] (Haegarda®) or lanadelumab-flyo (Takhzyro®) are considered medically necessary for prophylaxis against angioedema attacks related to HAE when ALL of the following criteria are met:

- Documented diagnosis of HAE as evidenced by:
 - Confirmed monoallelic mutation known to cause HAE in either the SERPING1 or F12 gene, OR
 - One C4 level below the lower limit of normal as defined by the laboratory performing the test AND EITHER:
 - C1 inhibitor (C1INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test OR

- C1INH functional level below the lower limit of normal as defined by the laboratory performing the test
- History of at least 2 moderate or severe attacks per month (for example airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion)
- Medications known to precipitate an attack (for example ACE-I, ARB, estrogens) have been evaluated and discontinued when appropriate
- Haegarda, and Takhzyro will not be used concomitantly
- Prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders

C1 Esterase Inhibitor [Human] ecallantide (Kalbitor®), icatibant (Firazyr®), icatibant (Sajazir™) are considered medically necessary for the treatment of acute angioedema attacks with HAE when ALL of the following criteria are met:

- Documented diagnosis of HAE as evidenced by:
 - Confirmed monoallelic mutation known to cause HAE in either the SERPING1 or F12 gene, OR
 - One C4 level below the lower limit of normal as defined by the laboratory performing the test AND EITHER:
 - C1 inhibitor (C1INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test OR
 - C1INH functional level below the lower limit of normal as defined by the laboratory performing the test
- History of moderate or severe attack (for example airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion)
- Medications known to precipitate an attack (for example ACE-I, ARB, estrogens) have been evaluated and discontinued when appropriate
- Will not be concomitantly administered with other approved treatments for acute HAE attacks (for example icatibant, Firazyr, Kalbitor, or Sajazir)
- Prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders

Coverage for Hereditary Angioedema (HAE) Therapy varies across plans. Refer to the customer’s benefit plan document for coverage details.

Where coverage requires the use of preferred products, the following criteria apply.

For Employer Group Plans and Individual and Family Plans, the following will apply in addition to criteria listed above:

Firazyr (Brand product)	<ul style="list-style-type: none"> • Documented intolerance to one generic formulation of icatibant (for example, Sajazir)
Kalbitor	<p>ONE of the following:</p> <ul style="list-style-type: none"> • Documented failure or inadequate response, contraindication per FDA label, intolerance or not a candidate (for example, age equal to or less than 18 years of age) for one generic formulation of icatibant • History of beneficial clinical response to Kalbitor

Initial authorization is up to 6 months

HAE agents are considered medically necessary for continued use when the following are met:

- Evidence of beneficial clinical response (for example, decrease in frequency of HAE acute attacks, decrease in HAE attack severity, decrease in duration of HAE attacks)
- Pretreatment clinical condition met the initial criteria for the specific drug
- For Takhzyro only: If the patient is attack free for more than 6 months an attempt, if clinically appropriate, to taper the dose to 300 mg every 4 weeks has been made

Reauthorization is up to 12 months

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Hereditary Angioedema Therapy is considered experimental, investigational or unproven for ANY other use including the following:

- Mild to Moderate Angiotensin Converting Enzyme Inhibitor-Induced Angioedema
- Acute ST Segment Elevation Myocardial Infarction - Emergency CABG

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indications

FDA Approved Indications

Brand Name	Approved Indication
Firazyr	Firazyr is a bradykinin B2 receptor antagonist indicated for the treatment of acute attacks of HAE in adults 18 years of age and older.
Haegarda	Haegarda is a plasma-derived concentrate of C1 Esterase Inhibitor (Human) (C1-INH) indicated for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients.
Kalbitor	Kalbitor is a plasma kallikrein inhibitor indicated for treatment of acute attacks of HAE in patients 12 years of age and older.
Sajazir	Sajazir is a bradykinin B2 receptor antagonist indicated for the treatment of acute attacks of HAE in adults 18 years of age and older.
Takhzyro	TAKHZYRO is a plasma kallikrein inhibitor (monoclonal antibody) indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older.

Recommended Dosing

FDA Recommended Dosing

Brand Name	Recommended Dosing
Firazyr	The recommended dose of Firazyr is 30 mg administered by subcutaneous (SC) injection in the abdominal area. Additional doses may be administered at intervals of at least 6 hours if response is inadequate or if symptoms recur. No more than 3 doses may be administered in any 24 hour period. Patients may self-administer Firazyr upon recognition of symptoms of an HAE attack after training under the guidance of a healthcare professional
Haegarda	Haegarda is intended for self-administration after reconstitution at a dose of 60 International Units (IU) per kg body weight by subcutaneous (S.C.) injection twice weekly (every 3 or 4 days).
Kalbitor	The recommended dose of Kalbitor is 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. Kalbitor should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema
Sajazir	The recommended dose of Sajazir is 30 mg administered by subcutaneous (SC) injection in the abdominal area. Additional doses may be administered at intervals of at least 6 hours if response is inadequate or if symptoms recur. No more than 3 doses may be administered in any 24 hour period.

Brand Name	Recommended Dosing
	Patients may self-administer Sajazir upon recognition of symptoms of an HAE attack after training under the guidance of a healthcare professional.
Takhzyro	Takhzyro is administered subcutaneously only and is intended for self-administration or administration by a caregiver. The recommended starting dose is 300 mg every 2 weeks. A dosing interval of 300 mg every 4 weeks is also effective and may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months.

Drug Availability

Brand Name	Drug Availability
Firazyr	Firazyr injection is supplied in a single-use, prefilled syringe delivering 30 mg icatibant. Each syringe delivers 3 mL solution with a concentration of 10mg/ml.
Haegarda	Haegarda is provided as a freeze-dried powder supplied in single-use vials containing 2000 or 3000 International Units (IU) of C1-INH for reconstitution with Sterile Water for Injection, USP.
Kalbitor	Kalbitor is supplied as three 10 mg/mL single-use vials packaged in a carton. Each vial contains 10 mg of ecallantide.
Sajazir	Sajazir injection is supplied in a single-use, prefilled syringe delivering 30 mg icatibant. Each syringe delivers 3 mL solution with a concentration of 10mg/ml.
Takhzyro	Takhzyro is a sterile, preservative-free, solution for injection in a single-dose glass vial. Each vial contains 300 mg/2 mL (150 mg/mL).

General Background

Disease Overview

Hereditary angioedema (HAE) is a rare autosomal dominant condition that is characterized by recurrent angioedema (most commonly in the extremities and face), intermittent abdominal pain and may be associated with a positive family history of a relative with similar symptoms. HAE can be difficult to discern from mast-cell mediated angioedema based on clinical presentation alone; however mast-cell mediated angioedema responds well to antihistamine and glucocorticoid treatments, whereas HAE does not. There are three types of HAE that have been defined at this time. HAE types I and II are caused by deficiency in the C1 esterase inhibitor (C1-INH), which leads to the overproduction of bradykinin and thus leads to an increase of vascular permeability. Individuals with HAE type III have normal levels of C1-INH protein and function; the mechanism(s) behind this disorder are less well understood, although 25% of cases are caused by mutations in the F12 gene. Most people with HAE experience acute attacks at some point in their lifetime, with onset any time after birth. All individuals with HAE are at risk for laryngeal edema, which can close the airway and become life-threatening. Therefore, it is important for individuals with HAE to be evaluated by a physician who has experience in treating HAE to establish an appropriate treatment plan to avoid life-threatening angioedema attacks (Farkas, 2016; Henao, 2016).

The diagnosis of HAE types I and II is typically made through blood tests for C4, C1-INH protein, C1-INH function and C1q complex. Individuals with HAE type I will have low levels of serum C4, low levels of C1-INH protein and function and normal C1q complex. A diagnosis of HAE type II is suspected for individuals with low serum C4 levels, normal or high C1-INH protein levels, low C1-INH function levels and normal C1q complex levels. For both disorders, these labs should be repeated 1-3 months after initial testing to confirm the diagnosis. The diagnostic criteria for HAE type III is not as well defined; an individual with a documented F12 mutation associated with the disorder meets criteria for the diagnosis but the diagnosis should also be considered for individuals with recurrent angioedema that does not respond to antihistamine therapy, normal C4 levels and normal C1-INH protein and function, and particularly in an individual with a positive family history (Henao, 2016).

The two most common types of HAE (I and II) are caused by a mutation in the SERPING1 gene. Approximately 85% of people with a diagnosis of HAE type I have identifiable missense, nonsense, deletion or insertion mutations. The remaining 15% of cases with SERPING1 mutations have HAE type II, which is caused by missense mutations in the active site of the gene. Approximately 25% of cases of

HAE types I and II are de novo. HAE type III has a likely autosomal dominant inheritance pattern with relatively low penetrance; 25% of these cases are caused by mutations in the F12 gene. The underlying cause for the remainder of cases of HAE type III is unknown at this time (Hena, 2016). Genetic testing for mutations in the SERPING1 and F12 genes is clinically available and can be useful in some Families (Farkas, 2016). Instances where genetic testing may be of benefit include:

- difficulty making a clinical diagnosis of HAE
- to aid in prenatal diagnosis
- in the diagnosis of a young child with symptoms (where enzyme testing may be inconclusive), typically prior to one year of age
- for first degree relatives of an individual with a diagnosis of HAE

At this time, there are no genotype-phenotype correlations that have demonstrated the ability to predict C1-INH functional activity or production, clinical severity, age of onset or response to treatment (Bafunno, 2014).

Therapy for HAE consists of long-term routine prophylaxis for patients with frequent or severe attacks, short-term prophylaxis for administration when a patient will be exposed to a known trigger (e.g., planned dental procedure), and rescue treatment for acute attacks (Bernstein, 2008; Epstein, 2008; Zuraw, 2008). Standard treatments for other types of angioedema (e.g., epinephrine, corticosteroids, and antihistamines) are not effective for treating HAE (Epstein, 2008). Antifibrinolytics (e.g., aminocaproic acid, tranexamic acid) and attenuated androgens (e.g., danazol, oxandrolone) are commonly used for prophylaxis or treatment of HAE. Danazol is FDA approved for the prevention of attacks of angioedema of all types (cutaneous, abdominal, and laryngeal) in males and females. Many patients either do not respond sufficiently to these agents or are unable to tolerate adverse events associated with their use. Fresh frozen plasma is also used for short-term prophylaxis or acute treatment for HAE attacks. C1-inhibitor products are used for long-term prophylaxis, short-term prophylaxis, and rescue treatment in other parts of the world (Bernstein, 2008; Bowen, 2010, 2008; Epstein, 2008; Gompels, 2005; Zuraw, 2008).

Pharmacology

The pharmacology for each HAE Therapy product is found in the following table:

Product	Pharmacology
Firazyr	Deficiency or dysfunction of C1-INH leads to increased levels of bradykinin in patients with HAE. Bradykinin causes smooth muscle contraction, increased vascular permeability, and vasodilatation. Firazyr selectively antagonizes the bradykinin type-2 receptor and inhibits inflammation during an HAE attack
Haegarda	C1-esterase inhibitor is a blood component which regulates the coagulation, complement, fibrinolytic, and kallikrein-kinin systems. Patients with HAE have decreased or absent C1-INH concentrations, or produce dysfunctional C1-INH. Haegarda is purified, human plasma-derived concentrate of C1-INH.
Kalbitor	Kalbitor is a potent, selective, reversible inhibitor of plasma kallikrein. Kalbitor binds to plasma kallikrein and blocks its binding site, inhibiting the conversion of HMW kininogen to bradykinin. By directly inhibiting plasma kallikrein, Kalbitor reduces the conversion of HMW kininogen to bradykinin and thereby treats symptoms of the disease during acute episodic attacks of HAE.
Sajazir	Deficiency or dysfunction of C1-INH leads to increased levels of bradykinin in patients with HAE. Bradykinin causes smooth muscle contraction, increased vascular permeability, and vasodilatation. Sajazir selectively antagonizes the bradykinin type-2 receptor and inhibits inflammation during an HAE attack.
Takhzyro	Lanadelumab-flyo is a fully human monoclonal antibody (IgG1/ κ -light chain) that binds plasma kallikrein and inhibits its proteolytic activity. Plasma kallikrein is a protease that cleaves high-molecular-weight-kininogen (HMWK) to generate cleaved HMWK (cHMWK) and bradykinin, a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with HAE. In patients with HAE due to C1-inhibitor (C1-INH) deficiency or dysfunction, normal regulation of plasma kallikrein activity is not present, which leads to uncontrolled increases in plasma kallikrein activity and results in angioedema attacks. Lanadelumab-flyo decreases

Product	Pharmacology
	plasma kallikrein activity to control excess bradykinin generation in patients with HAE.

Professional Societies/Organizations

Guidelines

Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma, and Immunology (ACAAI) and the Joint Council of Allergy, Asthma and Immunology

The Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma, and Immunology (ACAAI) and the Joint Council of Allergy, Asthma and Immunology, developed a focused parameter update on hereditary angioedema (HAE), acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. The Joint Task Force has published a recurrent angioedema diagnostic algorithm that may aid in accurately diagnosing HAE. Due to the potential for ex-vivo C4 degradation leading to an artificially low C4 level, it is recommended to repeat positive test results to confirm diagnosis. For acute attacks, on-demand treatment with a plasma-derived C1-INH, icatibant, or ecallantide is preferred as early as possible. Treatment with epinephrine, corticosteroids, antihistamines, attenuated androgens and antifibrinolytic agents are ineffective, and while fresh frozen plasma can be successful, there is a risk of viral transmission. For short-term prophylaxis, fresh frozen plasma, C1-INH replacement, or short-term, high-dose anabolic androgen therapy can be utilized. Long-term prophylaxis options include low-to-moderate doses of anabolic androgens (effective and relatively safe long-term), antifibrinolytic agents (less effective than androgens and relatively safe long-term), and plasma derived C1-INH (effective and safe long-term). For long-term prophylaxis, none of the available treatment modalities are given a preference with a notation that cost utility and cost-effectiveness studies are needed to guide management (Zuraw, 2013a).

US Hereditary Angioedema Association Medical Advisory Board

The US Hereditary Angioedema Association Medical Advisory Board (US HAE-MAB) published recommendations for management. This group recommends that all patients with HAE have access to at least 2 standard doses of therapy to treat acute attacks on-demand. Short-term prophylaxis may be indicated prior to medical, surgical, or dental procedures and treatment options include C1-INH administered 1-12 hours before stressor or anabolic androgens started 7-10 days before stressor. Decisions regarding use of long-term prophylaxis are dependent on the needs of the individual patient. While the US HAE-MAB notes that anabolic androgens have been used successfully for prophylaxis, there are potential significant adverse effects associated with therapy and that androgen therapy should not be used in patients interested in another treatment. In addition, they do not recommend requiring failure of androgen therapy in order to receive C1-INH therapy for prophylaxis. While noting that C1-inhibitor is safe and effective for prophylaxis, repeated intravenous administration can increase the risk of losing readily accessible venous access (Zuraw, 2013b).

World Allergy Organization (WAO) and European Academy of Allergy and Clinical Immunology (EAACI)

The World Allergy Organization (WAO) and European Academy of Allergy and Clinical Immunology (EAACI) published revised guidelines for the management of hereditary angioedema in 2017. For on-demand treatment (for example, acute attacks), WAO/EAACI recommends treatment with C1-INH, ecallantide, or icatibant and having and carrying treatment for 2 attacks. WAO/EAACI recommends against treatment with oral antifibrinolytics for on-demand treatment. They recommend consideration of short-term prophylaxis prior to surgeries (for example, dental/intraoral, where endotracheal intubation is required, where upper airway or pharynx is manipulated, before bronchoscopy or endoscopy) and promote use of C1-INH. Androgens could be used for short-term prophylaxis when surgery-related risk is low and C1-INH is not available. Tranexamic acid is mentioned as being used in the past for short-term prophylaxis, but WAO/EAACI notes that the efficacy is low. For long-term prophylaxis, WAO/EAACI recommends the use of C1-inhibitors as first-line and suggests the use of androgens (danazol) as second-line long-term prophylaxis. WAO/EAACI recommends against the use of antifibrinolytics for long-term prophylaxis. If androgen therapy is selected, it is recommended for laboratory monitoring every 6 months and a liver ultrasound annually. With regards to pregnancy, WAO/EAACI recommend C1-INH as the preferred therapy for HAE attacks during pregnancy and lactation (Evidence grade: D, strength of recommendation: strong). (Maurer, 2017).

Concerning long-term prophylaxis, there is disagreement between the organizations regarding which agent is preferred. While the US HAE-MAB notes that androgens are effective, they recommend against requiring the use of androgens if the patient expresses a preference for alternative therapy. However, the Joint Task Force on Practice Parameters (representing the AAAI, ACAAI, and the JCAAI) recommends either androgen therapy or C1-INH without placing a preference of one over the other. The WAO/EAACI revised their position in 2017, and lists C1-inhibitor therapy as first-line, followed by attenuated androgens as second-line.

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

No recommendations are available for Hereditary Angioedema (HAE) therapies.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)

There are no CMS National Coverage Determinations for Firazyr, Haegarda, Kalbitor, Sajazir or Takhzyro.

Clinical Efficacy

The COMPACT trial evaluated the safety and efficacy of Haegarda for the prophylaxis of HAE attacks. This randomized, placebo-controlled, crossover study evaluated the efficacy of Haegarda 40 IU/kg and Haegarda 60 IU/kg compared to placebo. The primary efficacy outcome was number of HAE attacks per month. Patients assigned to Haegarda 40 IU/kg experienced an average of 2.42 fewer attacks (95% CI, 1.46-3.38; $P < 0.001$) compared to placebo. Patients assigned to Haegarda at the labeled dosage had an average of 3.51 fewer attacks (95% CI, 2.81-4.21; $P < 0.001$) compared to placebo (Longhurst, 2017).

Three published, randomized, controlled trials compared with placebo for acute treatment of a single HAE attack. The median time to sustained symptom relief was 66 to 122 minutes with compared with 303 to 495 minutes with placebo ($p \leq 0.013$) (Reidl, 2014 and Zuraw, 2010b). No trials have compared with another C1-esterase inhibitor product or with any other agent used for treating acute HAE attacks.

Off Label Uses

AHFS Drug Information 2019 Edition does not support any off-label uses of Firazyr, Haegarda, Kalbitor, Sajazir or Takhzyro.

Experimental, Investigational, Unproven Uses

Mild to Moderate Angiotensin Converting Enzyme Inhibitor – Induced Angioedema

Studies have reported that there were no significant improvement and/or studies were limited by small and/or heterogeneous patient populations; short-term follow-ups; lack of a control group; potential reporting and publication bias; and heterogeneity of inclusion criteria. (Lewis, 2015)

Acute ST Segment Elevation Myocardial Infarction - Emergency CABG

There is insufficient evidence in the peer-reviewed published scientific literature to support safety and efficacy of Haegarda in the prophylaxis of Acute ST segment elevation myocardial infarction – Emergency CABG.

Coding/ Billing Information

Note: Icatibant (Firazyr, Sajazir), Haegarda, and lanadelumab-flyo (Takhzyro) are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions. Human and Recombinant C1 Esterase Inhibitor require medical drug coding and are listed as follows:

- Note:**
- 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.

Covered when medically necessary:

HCPCS Codes	Description
J1290	Injection, ecallantide, 1 mg

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