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PHARMACY / MEDICAL POLICY – 5.01.587

Hereditary Angioedema

Effective Date:	**Jul. 1, 2025***
Last Revised:	Jun. 10, 2025
Replaces:	N/A

*This policy has been revised. Click here to view the changes effective October 3, 2025.

RELATED MEDICAL POLICIES:
None

The Site of Service Medical Necessity criteria within this policy DOES NOT apply to Alaska fully-insured members; refer to the infusion drug Medical Necessity criteria only.

Site of Service *and* the infusion drug Medical Necessity criteria apply to all other plan members.

Please contact Customer Service for more information.

Select a hyperlink below to be directed to that section.

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Introduction

Hereditary angioedema (HAE) is an inherited condition. Individuals have unpredictable attacks with swelling, pain and inflammation in various parts of the body. These episodes are painful and in some cases life threatening because the swelling may block the person's ability to breathe. HAE affects about one in 50,000 people. There are different types of HAE, and the effects may be more severe in different individuals.

The unpredictability of these attacks is a serious problem. About half of individuals with HAE will have at least one attack with life threatening throat swelling at some point in their lives. A recent survey of 457 individuals with HAE reported an average of around 25 acute attacks per year. A typical attack lasts 2 to 5 days.[10]

HAE is caused by a defect in the gene that produces an enzyme called C1 esterase inhibitor that is normally in blood plasma. Drugs that treat HAE either replace the missing enzyme or affect

other parts of the process that causes the attacks. This policy describes when these types of drugs may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Site of Service (SOS) Medical Necessity criteria applies ONLY to medical benefit reviews. SOS Medical Necessity criteria does NOT apply to Alaska fully-insured members; refer to the infusion drug Medical Necessity criteria only. Please contact Customer Service for more information.

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those aged 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home.

Drugs subject to site of service review addressed in this policy are:

- Cinryze (pdC1-INH)

Site of Service Administration	Medical Necessity
Medically necessary sites of service • **Physician's office** • **Infusion center** • **Home infusion**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site:** • These are the preferred **medically necessary** sites of service for specified drugs.

Site of Service Administration	Medical Necessity
Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.** **This site is considered medically necessary for the first 90 days for the following:** • The initial course of infusion of a pharmacologic or biologic agent **OR** • Re-initiation of an agent after 6 months or longer following discontinuation of therapy* **Note:** *This does not include when standard dosing between infusions is 6 months or longer **This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the individual's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.** **This site is considered medically necessary only when the individual has a clinical condition which puts him or her at increased risk of complications for infusions, including any 1 of the following:** • Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, %FVC less than or equal to 40%) that may increase the risk of an adverse reaction • Unstable renal function which decreases the ability to respond to fluids • Difficult or unstable vascular access • Acute mental status changes or cognitive conditions that impact the safety of infusion therapy

Site of Service Administration	Medical Necessity

	• A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug
	
	This site is considered medically necessary when the individual has cytokine release syndrome (CRS) and all the following are met:
	• CRS is grade 3 or 4 as evidenced by ALL the following:
	  ○ Temperature at least 38 °C
	  ○ Hypotension that requires 1 or more vasopressors
	  ○ Hypoxia that requires oxygen through a high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask OR positive pressure (continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, or mechanical ventilation)
	AND
	• The individual will be admitted into an inpatient setting as soon as possible

Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.**

Drug	Medical Necessity

Berinert (pdC1-INH) IV
 	
Managed under medical benefit
	Berinert (pdC1-INH) may be considered medically necessary for treatment of acute attacks of angioedema in adult and pediatric individuals:
	• With type I hereditary angioedema (HAE) established by ALL the following documented laboratory values:
	  ○ *Low complement component 4 (C4) levels
	  ○ *Low C1 esterase inhibitor (C1-INH) protein (antigenic) levels
	OR

Drug	Medical Necessity

	• With type II HAE established by ALL the following documented laboratory values:
	  ○ *Low C4 levels
	  ○ Normal or high C1-INH protein (antigenic) levels
	  ○ *Low C1-INH functional levels
	OR
	• With acquired angioedema established by ALL the following documented laboratory values:
	  ○ *Low complement component 1q (C1q) levels
	  ○ *Low C4 levels
	  ○ *Low C1-INH protein (antigenic) levels
	  ○ *Low C1-INH functional levels
	AND
	• Has 2 or more of the following clinical features:
	  ○ Recurrent angioedema without wheals or urticaria
	  ○ Recurrent abdominal attacks
	  ○ Positive family history
	  ○ Failure to respond to antihistamines, glucocorticoids, or epinephrine
	AND
	• If aged 18 years or older and not currently pregnant, has tried and had an inadequate response or intolerance to generic icatibant
	AND
	• Treatment is not used concomitantly with other targeted HAE-specific therapies for acute treatment
	
	Note: *Low is below the lower limit of normal as defined by the laboratory test.

Cinryze (pdC1-INH) IV **Managed under medical benefit**	**Cinryze (pdC1-INH) IV is subject to review for site of service administration.** **Cinryze (pdC1-INH) may be considered medically necessary for the long-term prophylaxis of acute angioedema attacks in:** • Individuals aged 6 years or older **AND**

Drug	Medical Necessity

	• With type I hereditary angioedema (HAE) established by ALL the following documented laboratory values:
	  ○ *Low complement component 4 (C4) levels
	  ○ *Low C1 esterase inhibitor (C1-INH) protein (antigenic) levels
	OR
	• With type II HAE established by ALL the following documented laboratory values:
	  ○ *Low C4 levels
	  ○ Normal or high C1-INH protein (antigenic) levels
	  ○ *Low C1-INH functional levels
	AND
	• Has 2 or more of the following clinical features:
	  ○ Recurrent angioedema without wheals or urticaria
	  ○ Recurrent abdominal attacks
	  ○ Positive family history
	  ○ Failure to respond to antihistamines, glucocorticoids, or epinephrine
	AND
	• 1 of the following:
	  ○ History of 1 or more HAE attacks a month over a 6-month period requiring acute treatment with Berinert, Firazyr, generic icatibant, Kalbitor, Ruconest, or Sajazir
	  OR
	  ○ Documentation of pregnancy
	  OR
	  ○ Documentation of laryngeal HAE attack within the last 5 years
	AND
	• Treatment is not used concomitantly with other targeted HAE-specific therapies for prophylactic treatment
	
	Note: *Low is below the lower limit of normal as defined by the laboratory test.

Icatibant, generic	**Generic icatibant may be considered medically necessary for treatment of acute attacks of angioedema in:** • Individuals aged 18 years or older

Drug	Medical Necessity

Managed under pharmacy and medical benefit	**AND**
	• With type I hereditary angioedema (HAE) established by ALL the following documented laboratory values:
	  ○ *Low complement component 4 (C4) levels
	  ○ *Low C1 esterase inhibitor (C1-INH) protein (antigenic) levels
	OR
	• With type II HAE established by ALL the following documented laboratory values:
	  ○ *Low C4 levels
	  ○ Normal or high C1-INH protein (antigenic) levels
	  ○ *Low C1-INH functional levels
	OR
	• With acquired angioedema established by ALL the following documented laboratory values:
	  ○ Low complement component 1q (C1q) levels*
	  ○ Low C4 levels*
	  ○ Low C1-INH protein (antigenic) levels*
	  ○ Low C1-INH functional levels*
	AND
	• Has 2 or more of the following clinical features:
	  ○ Recurrent angioedema without wheals or urticaria
	  ○ Recurrent abdominal attacks
	  ○ Positive family history for type I HAE or type II HAE
	  ○ Failure to respond to antihistamines, glucocorticoids, or epinephrine
	AND
	• Treatment is not used concomitantly with other targeted HAE-specific therapies for acute treatment
	
	***Note:** Low is below the lower limit of normal as defined by the laboratory test.

• **Firazyr (icatibant) SC** • **Sajazir (icatibant) SC** **Managed under pharmacy and medical benefit**	**Firazyr (icatibant) and Sajazir (icatibant) may be considered medically necessary for treatment of acute attacks of angioedema in:** • Individuals aged 18 years or older **AND**

Drug	Medical Necessity

	• With type I hereditary angioedema (HAE) established by ALL the following documented laboratory values:
	  ○ Low complement component 4 (C4) levels*
	  ○ Low C1 esterase inhibitor (C1-INH) protein (antigenic) levels*
	OR
	• With type II HAE established by ALL the following documented laboratory values:
	  ○ Low C4 levels*
	  ○ Normal or high C1-INH protein (antigenic) levels
	  ○ Low C1-INH functional levels*
	OR
	• With acquired angioedema established by ALL the following documented laboratory values:
	  ○ Low complement component 1q (C1q) levels*
	  ○ Low C4 levels*
	  ○ Low C1-INH protein (antigenic) levels*
	  ○ Low C1-INH functional levels*
	AND
	• Has 2 or more of the following clinical features:
	  ○ Recurrent angioedema without wheals or urticaria
	  ○ Recurrent abdominal attacks
	  ○ Positive family history for type I HAE or type II HAE
	  ○ Failure to respond to antihistamines, glucocorticoids, or epinephrine
	AND
	• If aged 18 years or older and not currently pregnant, has tried and had an inadequate response or intolerance to generic icatibant
	AND
	• Treatment is not used concomitantly with other targeted HAE-specific therapies for acute treatment
	
	***Note:** Low is below the lower limit of normal as defined by the laboratory test.

Haegarda (pdC1-INH) SC	**Haegarda (pdC1-INH) may be considered medically necessary for the long-term prophylaxis of acute angioedema attacks in:**

Drug	Medical Necessity

Managed under pharmacy and medical benefit	• Individuals aged 6 years or older
	AND
	• With type I hereditary angioedema (HAE) established by ALL the following documented laboratory values:
	  ○ Low complement component 4 (C4) levels*
	  ○ Low C1 esterase inhibitor (C1-INH) protein (antigenic) levels*
	OR
	• With type II HAE established by ALL the following documented laboratory values:
	  ○ Low C4 levels*
	  ○ Normal or high C1-INH protein (antigenic) levels
	  ○ Low C1-INH functional levels*
	AND
	• Has 2 or more of the following clinical features:
	  ○ Recurrent angioedema without wheals or urticaria
	  ○ Recurrent abdominal attacks
	  ○ Positive family history
	  ○ Failure to respond to antihistamines, glucocorticoids, or epinephrine
	AND
	• 1 of the following:
	  ○ History of 1 or more HAE attacks a month over a 6-month period requiring acute treatment with Berinert, Firazyr, generic icatibant, Kalbitor, Ruconest, or Sajazir
	  OR
	  ○ Documentation of pregnancy
	  OR
	  ○ Documentation of laryngeal HAE attack within the last 5 years
	AND
	• Treatment is not used concomitantly with other targeted HAE-specific therapies for prophylactic treatment
	
	***Note:** Low is below the lower limit of normal as defined by the laboratory test.

Drug	Medical Necessity

Kalbitor (ecallantide) SC
 	
Managed under pharmacy and medical benefit
	Kalbitor (ecallantide) may be considered medically necessary for treatment of acute attacks of angioedema in:
	• Individuals aged 12 years or older
	AND
	• With type I hereditary angioedema (HAE) established by ALL the following documented laboratory values:
	  ○ Low complement component 4 (C4) levels*
	  ○ Low C1 esterase inhibitor (C1-INH) protein (antigenic) levels*
	OR
	• With type II HAE established by ALL the following documented laboratory values:
	  ○ Low C4 levels*
	  ○ Normal or high C1-INH protein (antigenic) levels
	  ○ Low C1-INH functional levels*
	OR
	• With acquired angioedema established by ALL the following documented laboratory values:
	  ○ Low complement component 1q (C1q) levels*
	  ○ Low C4 levels*
	  ○ Low C1-INH protein (antigenic) levels*
	  ○ Low C1-INH functional levels*
	AND
	• Has 2 or more of the following clinical features:
	  ○ Recurrent angioedema without wheals or urticaria
	  ○ Recurrent abdominal attacks
	  ○ Positive family history for type I HAE or type II HAE
	  ○ Failure to respond to antihistamines, glucocorticoids or epinephrine
	AND
	• Treatment is to be administered by a healthcare professional with appropriate medical support to manage anaphylaxis
	AND
	• If aged 18 years or older and not currently pregnant, has tried and had an inadequate response or intolerance to generic icatibant
	AND

Drug	Medical Necessity
	• Treatment is not used concomitantly with other targeted HAE-specific therapies for acute treatment *__Note:__ Low is below the lower limit of normal as defined by the laboratory test.

Orladeyo (berotralstat) oral
 	
Managed under pharmacy benefit
	Orladeyo (berotralstat) may be considered medically necessary for the long-term prophylaxis of acute angioedema attacks in:
	• Individuals aged 12 years or older
	AND
	• With type I hereditary angioedema (HAE) established by ALL the following documented laboratory values:
	  ○ Low complement component 4 (C4) levels*
	  ○ Low C1 esterase inhibitor (C1-INH) protein (antigenic) levels*
	OR
	• With type II HAE established by ALL the following documented laboratory values:
	  ○ Low C4 levels*
	  ○ Normal or high C1-INH protein (antigenic) levels
	  ○ Low C1-INH functional levels*
	AND
	• Has 2 or more of the following clinical features:
	  ○ Recurrent angioedema without wheals or urticaria
	  ○ Recurrent abdominal attacks
	  ○ Positive family history
	  ○ Failure to respond to antihistamines, glucocorticoids, or epinephrine
	AND
	• 1 of the following:
	  ○ History of 1 or more HAE attacks a month over a 6-month period requiring acute treatment with Berinert, Firazyr, generic icatibant, Kalbitor, Ruconest, or Sajazir
	  OR
	  ○ Documentation of pregnancy
	  OR
	  ○ Documentation of laryngeal HAE attack within the last 5 years

Drug	Medical Necessity
	AND • Treatment is not used concomitantly with other targeted HAE-specific therapies for prophylactic treatment **AND** • Dose prescribed is limited to 150 mg per day *__Note:__ Low is below the lower limit of normal as defined by the laboratory test.

Ruconest (rhC1-INH) IV
 	
Managed under medical benefit
	Ruconest (rhC1-INH) may be considered medically necessary for treatment of acute attacks of angioedema in:
	• Individuals aged 13 years or older
	AND
	• With type I hereditary angioedema (HAE) established by ALL the following documented laboratory values:
	  ○ Low complement component 4 (C4) levels*
	  ○ Low C1 esterase inhibitor (C1-INH) protein (antigenic) levels*
	OR
	• With type II HAE established by ALL the following documented laboratory values:
	  ○ Low C4 levels*
	  ○ Normal or high C1-INH protein (antigenic) levels
	  ○ Low C1-INH functional levels*
	AND
	• Has 2 or more of the following clinical features:
	  ○ Recurrent angioedema without wheals or urticaria
	  ○ Recurrent abdominal attacks
	  ○ Positive family history
	  ○ Failure to respond to antihistamines, glucocorticoids or epinephrine
	AND
	• If aged 18 years or older and not currently pregnant, has tried and had an inadequate response or intolerance to generic icatibant
	AND
	• Treatment is not used concomitantly with other targeted HAE-specific therapies for acute treatment

Drug	Medical Necessity
	*__Note__: Low is below the lower limit of normal as defined by the laboratory test.

Takhzyro (lanadelumab-flyo) SC
 	
Managed under pharmacy and medical benefit
	Takhzyro (lanadelumab-flyo) may be considered medically necessary for the long-term prophylaxis of acute angioedema attacks in:
	• Individuals aged 2 years or older
	AND
	• With type I hereditary angioedema (HAE) established by ALL the following documented laboratory values:
	  ○ Low complement component 4 (C4) levels*
	  ○ Low C1 esterase inhibitor (C1-INH) protein (antigenic) levels*
	OR
	• With type II HAE established by ALL the following documented laboratory values:
	  ○ Low C4 levels*
	  ○ Normal or high C1-INH protein (antigenic) levels
	  ○ Low C1-INH functional levels*
	AND
	• Has 2 or more of the following clinical features:
	  ○ Recurrent angioedema without wheals or urticaria
	  ○ Recurrent abdominal attacks
	  ○ Positive family history
	  ○ Failure to respond to antihistamines, glucocorticoids or epinephrine
	AND
	• 1 of the following:
	  ○ History of 1 or more HAE attacks a month over a 6-month period requiring acute treatment with Berinert, Firazyr, generic icatibant, Kalbitor, Ruconest, or Sajazir
	  OR
	  ○ Documentation of pregnancy
	  OR
	  ○ Documentation of laryngeal HAE attack within the last 5 years
	AND

Drug	Medical Necessity
	• Treatment is not used concomitantly with other targeted HAE-specific therapies for prophylactic treatment **AND** • Dose prescribed is limited to 300 mg every 2 weeks * **Note:** Low is below the lower limit of normal as defined by the laboratory test.

Drug	Investigational
As listed	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.** **All other reviews all drugs listed in policy may be approved up to 3 months.**
Reauthorization criteria	**Non-formulary exception reviews and all other reviews for all drugs listed in the policy may be approved up to 12 months if the above conditions are met, and the individual has shown and continues to show a reduction in baseline frequency of attacks for long-term prophylaxis drugs or duration and severity of attacks for acute treatment drugs.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the relevant history and physical **AND** • Applicable laboratory testing results

Coding

Code	Description
HCPCS	
J0593	Injection, lanadelumab-flyo (Takhzyro), 1 mg (code may be used for Medicare when drug administered under direct supervision of a physician, not for use when drug is self-administered)
J0596	Injection, C1 esterase inhibitor (recombinant), Ruconest, 10 units
J0597	Injection, C-1 esterase inhibitor (human), Berinert, 10 units
J0598	Injection, C-1 esterase inhibitor (human), Cinryze, 10 units
J0599	Injection, c-1 esterase inhibitor (human), (Haegarda), 10 units
J1290	Injection, ecallantide (Kalbitor), 1 mg
J1744	Injection, icatibant, 1 mg (used to report Firazyr, Sajazir and generic icatibant)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Consideration of Age

Minimum age for treatment with each of the above drugs is determined according to the labeled indication.

For site of service for medical necessity the age described in this policy is 13 years of age or older. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home. The age criterion for site of service for medical necessity is based on the following: Pediatric individuals are not small adults. Pediatric individuals differ physiologically, developmentally, cognitively, and emotionally from adult individuals, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV

insertions and therapy. Due to pediatrics unique physiology and psychology, site of service review is limited to individuals above the age of 13.

Benefit Application

Orladeyo (berotralstat) is managed through the pharmacy benefit. Firazyr (icatibant), generic icatibant, Haegarda (pdC1-INH), Kalbitor (ecallantide), Sajazir (icatibant), and Takhzyro (lanadelumab-flyo) are managed through both the pharmacy and medical benefit. Berinert (pdC1-INH), Cinryze (pdC1-INH), and Ruconest (rhC1-INH) are managed through the medical benefit.

Evidence Review

Description

HAE is an autosomal dominant disorder characterized by unpredictable intermittent edema, inflammation, and pain particularly in the skin, gastrointestinal tract, genitals, face, and upper airways. There are two major types of HAE, called type I and type II, and one minor type called type III. Type I is characterized by insufficient production of C1 esterase inhibitor and comprises approximately 80-85% of all cases. Type II is characterized by normal or high production of functionally deficient C1 inhibitor and comprises most of the rest of cases. Type III is very rare, occurring in < 1% of individuals. Type III is characterized by normal production of functionally deficient C1 inhibitor but also appears to be X-linked.

Disease Burden

HAE is an orphan condition, with an estimated prevalence of 1 in 10,000 to 1 in 50,000. All races and both genders are affected equally. Frequency, severity, and duration of attacks can vary considerably between affected individuals. Laryngeal attacks can be fatal if not treated in time to prevent asphyxiation.

It is estimated that approximately 52% of individuals experience laryngeal attacks at some point in their lives while recurrent abdominal attacks due to gastrointestinal (GI) wall edema are reported to affect up to 94% of individuals. In a recent survey of 457 individuals with HAE, a

mean of 26.9 and a median of 12.0 acute attacks per year were reported. A typical attack lasts 2 to 5 days.

In a US burden of illness study, the direct and indirect average annual costs to manage one HAE individual were $25,884 and $16,108, respectively, in 2007 US dollars.[14] Medical treatment for acute attacks accounted for a majority (82%) of the direct costs. When stratified by severity of HAE events, annual direct costs ranged from $14,350 for mild attacks, $26,900 for moderate attacks, and $95,500 for severe attacks.

Pathophysiology

C1 esterase inhibitor is a normal component of human plasma and is a serine protease inhibitor (serpin). Serpins form irreversible bonds with proteases they inactivate. As with other serpins, C1 esterase inhibitor has an important regulatory function on several of the major cascade systems of the human body, including the complement system, the intrinsic coagulation (contact) system, the fibrinolytic system, and the coagulation cascade. C1 esterase inhibitor is the only known inhibitor for the following substrates: complement component 1 (C1r and C1s), coagulation factor XIIa, and kallikrein. Additionally, it is the main inhibitor for coagulation factor XIa in the intrinsic coagulation cascade.

HAE individuals have low levels of endogenous or functional C1 esterase inhibitor. Although the events that induce attacks of angioedema in HAE individuals are not well established, it is believed that the increased vascular permeability and the clinical manifestation of HAE attacks are primarily mediated through contact system activation and the generation of bradykinin. Suppression of contact system activation by C1 esterase inhibitor is primarily mediated through inactivation of plasma kallikrein and factor XIIa. Other current therapeutic options for this condition mediate their activity through direct antagonism of bradykinin or kallikrein inhibition.

Treatment Alternatives

Acute attacks of hereditary angioedema do not respond to traditional treatments for hypersensitivity reactions (i.e., antihistamines, epinephrine, and corticosteroids) because these treatments target mast-cell mediated sequelae (i.e., due to histamine release), as opposed to sequelae of kallikrein-mediated bradykinin formation.[14]

The treatment options for HAE are usually divided into three categories: chronic long-term prophylaxis to reduce the frequency and severity of attacks, short-term prophylaxis to prevent

attacks with known exposure to possible triggers (e.g., surgery or dental procedures), and on-demand treatment of acute attacks. Androgenic steroids were the first drug class approved for use for this condition in the US. Danazol is labeled for the prevention of attacks of angioedema. The drug is also used for chronic long-term prophylaxis. Stanozolol was also approved with a similar indication, but this agent is no longer marketed in the US. Oxandrin (oxandrolone) and methyltestosterone have been used off-label for long-term HAE attack prophylaxis.

Over the last 15 years, eight new drugs/biologics were approved for HAE, all with slightly different indications. In 2008 Cinryze, a human plasma-derived C1-INH was approved for prophylaxis of HAE attacks. In 2009 Berinert, human plasma-derived C1-INH was approved for the treatment of acute abdominal or facial attacks of HAE and Kalbitor (ecallantide), an inhibitor of human plasma kallikrein, was approved for the treatment of acute attacks of HAE. In 2011 Firazyr (icatibant), a bradykinin type 2 receptor blocker, was approved for the treatment of acute attacks of HAE. In 2014 Ruconest, a C1 esterase inhibitor, was approved for the treatment of acute attacks in adult and adolescent individuals with HAE. In 2017 Haegarda, a human plasma-derived C1-INH was approved for the routine prophylaxis of HAE attacks. In 2018 Takhzyro, a plasma kallikrein inhibitor (monoclonal antibody), was approved for the prophylactic treatment of HAE in individuals 12 years and older. In 2020 Orladeyo (berotralstat), an oral plasma kallikrein inhibitor, was approved for the prophylactic treatment of HAE in individuals 12 years and older

Preferred Existing Therapy

The 2021 revision for the international World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) guideline for the management of hereditary angioedema recommends that HAE attacks are treated with either intravenous C1-INH, ecallantide, or icatibant. Individuals should also have sufficient medication for on-demand treatment of at least two attacks and carry on-demand medication at all times.

For short-term/procedural prophylaxis the WAO/EAACI guidelines recommend considering short-term prophylaxis before procedures that can induce an attack and recommends the use of intravenous plasma-derived C1 inhibitor as first-line short-term prophylaxis. For long-term prophylaxis they recommend the use of C1-INH, lanadelumab, and berotralstat for first-line long-term prophylaxis and to use androgens as second-line long-term prophylaxis. Androgens are second-line as they have significant side effects and are contraindicated in pregnancy. In addition, androgens should be avoided in pre-pubertal children (male and female) and post-pubertal girls.

For children with HAE the WAO/EAACI recommends testing children from HAE-affected families be carried out as soon as possible and all offspring of an affected parent be tested. For treatment the recommendation is to use C1-INH or icatibant for the treatment of HAE attacks in children under the age of 12.

For therapy of HAE in pregnant and breastfeeding individuals with HAE the WAO/EAACI recommends plasma-derived C1 inhibitor as the preferred therapy during pregnancy and lactation.

Table 1. Comparison of Targeted HAE-specific Treatments

Drug	FDA-approved Indication	Mechanism of Action	Dose / Route	Time to Onset of Relief (Duration)	Serious Adverse Effects
Berinert	Acute abdominal, facial, or laryngeal attacks (no lower age limit)	pdC1-INH replacement	On demand: 20 U/kg IV (1500 U) *Prophylaxis: 10-30 U/kg IV pre-procedure or 1-2 times/week (1500 units BIW)	Median: 0.8 hrs (22 hrs)	Rare: anaphylaxis, thrombosis Theoretical: blood-borne infections
Ruconest	Acute HAE attacks in patients ≥13 yrs of age	rhC1-INH replacement	On demand: 50 U/kg IV (4200 U) *Prophylaxis: N/A	Median: 1.5 hrs (10 hrs)	Rare: hypersensitivity (rabbit-sensitized)
Cinryze	Prophylaxis of HAE attacks in patients ≥6 yrs of age	pdC1-INH replacement	*On-demand: 1000 U IV, if needed repeat x 1 after 1 hr Prophylaxis: 1000 U IV BIW	Median: 0.5 hrs (56 hrs)	Rare: anaphylaxis, thrombosis Theoretical: blood-borne infections
Haegarda	Prophylaxis of HAE attacks in patients ≥6 yrs of age	pdC1-INH replacement	*On-demand: N/A Prophylaxis: 60 IU/kg SC BIW	Median: N/A (N/A)	Rare: hypersensitivity Theoretical: thrombosis, blood-borne infections

Drug	FDA-approved Indication	Mechanism of Action	Dose / Route	Time to Onset of Relief (Duration)	Serious Adverse Effects
Kalbitor	Acute HAE attacks in patients ≥12 yrs of age	Plasma kallikrein inhibitor	On-demand: 30 mg SC *Prophylaxis: N/A	Median: 1 hr (4-10 hrs)	Uncommon: anaphylaxis, development of anti-C1-INH antibodies (must be administered by a health professional)
Takhzyro	Prophylaxis of HAE attacks in patients ≥12 yrs of age	Plasma kallikrein inhibitor	*On-demand: N/A Prophylaxis: 300 mg SC Q2W	Median: N/A (N/A)	N/A
Firazyr, Sajazir	Acute HAE attacks in patients ≥18 yrs of age	Bradykinin-2 receptor antagonist	On-demand: 30 mg SC *Prophylaxis: N/A	Median: 2 hrs (6 hrs)	Theoretical: Worsening of an ongoing ischemic event
Orladeyo	Prophylaxis of HAE attacks in patients ≥12 yrs of age	Plasma kallikrein inhibitor	150 mg orally once daily	Median: N/A (N/A)	QT prolongation > 150 mg dose

Key: *Off-label use; BIW = twice weekly, C1-INH = C1 esterase inhibitor, HAE = hereditary angioedema, IV = intravenously, N/A = not available, pd = plasma derived, SC = subcutaneously, rh = recombinant human, U = units
All dosing scenarios assume for an 80 kg adult. Dose may be rounded to nearest full vial size.

Summary of Evidence

Efficacy of Lanadelumab

The efficacy of lanadelumab for the prevention of angioedema attacks in individuals ≥12 years of age with type I or II HAE was demonstrated in one moderate-to-good quality phase 3, randomized, double-blind, parallel-group, placebo-controlled clinical trial (HELP). A total of 125 individuals with a baseline attack frequency of ≥1 attack/month received lanadelumab 150 mg SC every 4 weeks (Q4W), 300 mg SC Q4W, 300 mg SC every 2 weeks (Q2W), or placebo (n=41) for 26 weeks. Outcomes evaluated included: 1) the number of angioedema attacks occurring during prophylaxis (primary endpoint), 2) the number of attacks requiring acute treatment

(secondary endpoint), and 3) the number of moderate to severe attacks (secondary endpoint). A significant reduction in the mean monthly attack rate for all primary and secondary endpoints occurred for all lanadelumab dosing regimens compared to placebo (all P<0.001). While the study did not appear to be designed to determine an optimal dosing regimen and the outcome confidence intervals overlap for the lanadelumab arms, the 300 mg SC Q2W dosing arm consistently had numerically better results.

Safety of Lanadelumab

Safety at presumed approved dosing (300 mg SC Q2W) in the target population was assessed in the phase 3 HELP study for up to 26 weeks (n=27) and in a phase 1b study for up to 50 days (n=5). No SAEs, deaths, or discontinuation due to AEs were reported in either study. Outside of angioedema attacks, the most commonly occurring AEs with lanadelumab were injection-site pain, injection-site erythema, and headache. Most AEs were mild to moderate in severity.

2019 Update

Reviewed prescribing information for all drugs listed in policy and conducted literature search on the diagnosis of HAE and acquired angioedema. Provided additional details on laboratory values and clinical features that support the diagnosis of HAE and acquired angioedema.

2020 Update

Reviewed prescribing information for all drugs listed in policy. Haegarda (pdC1-INH) prescribing information was updated from individuals ≥12 years of age to individuals ≥6 years of age. Added information to Evidence Review from the 2017 revision for the international World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) guideline for the management of hereditary angioedema.

2021 Update

Reviewed prescribing information for all drugs listed in policy and checked for updated guidelines on treatment for acute angioedema attacks and long-term prophylaxis. No changes were identified that would impact policy statements.

2022 Update

Reviewed prescribing information for all drugs listed in policy and reviewed product availability. Added a new generic product identified called Sajazir (icatibant) with the identical coverage criteria as generic icatibant. Reviewed "The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update". Based on guidelines, the information listed for the preferred existing therapies section in policy were updated, but no guideline changes were identified that would impact the policy statements.

2023 Update

Reviewed prescribing information for all drugs listed in policy and reviewed product availability. Updated Takhzyro coverage criteria from individuals 12 years of age and older to individuals 2 years of age and older.

2024 Update

Reviewed prescribing information for all drugs listed in policy and reviewed product availability. Removed requirement to try Danocrine (danazol) or another androgen for adult males from Haegarda (pdC1-INH), Orladeyo (berotralstat), Takhzyro (lanadelumab), and Cinrzye (pdC1-INH). Updated Berinert (pDC1-INH), Kalbitor (ecallantide), and Ruconest (rhC1-INH) to require trial with generic icatibant or Sajazir (icatibant).

2025 Update

Reviewed prescribing information for all drugs listed in policy and reviewed product availability. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members pursuant to **Alaska HB 226** (accessed January 3, 2025). Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS). Removed Sajazir (icatibant) as a preferred treatment for acute

attacks of hereditary angioedema. Updated Berinert (pdC1-INH), Firazyr (icatibant), Kalbitor (ecallantide), and Ruconest (rhC1-INH) coverage criteria to clarify that the generic icatibant step therapy requirement applies to individuals aged 18 years or older who are not currently pregnant.

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19. Haegarda (C1 esterase inhibitor subcutaneous [human]) prescribing information. CSL Behring; Kankakee, IL. Revised January 2022.
20. Kalbitor (ecallantide) prescribing information. Dyax Corp.; Lexington, MA. Revised November 2021.
21. Orladeyo (berotralstat) prescribing information. BioCryst Pharmaceuticals, Inc.; Durham, NC. Revised October 2024.
22. Ruconest (C1 esterase inhibitor [recombinant]) prescribing information. Pharming Healthcare Inc.; Warren, NJ. Revised April 2020.
23. Sajazir (icatibant) prescribing information. Cycle Pharmaceuticals Ltd.; Cambridge, United Kingdom. Revised February 2024.
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History

Date	Comments
11/01/18	New policy, approved October 9, 2018, effective February 1, 2019. Added codes J0596, J0597, J0598, J1290, J1744, and J3490.
12/20/18	Interim Review, approved December 19, 2018. Criteria for drugs managed through the pharmacy benefit were removed from this policy and added to new policy 5.01.594.
02/01/19	Contents from policy 5.01.594 moved back to this policy. Added HCPCS code J0599.
04/01/19	Interim Review, approved March 19, 2019. Updated criteria for Cinryze, Firazyr, Haegarda, Kalbitor and Takhzyro.
08/01/19	Annual Review, approved July 25, 2019. Added generic icatibant to policy with identical criteria as Firazyr. Provided additional details on laboratory values and clinical features that support the diagnosis of HAE and acquired angioedema. Removed HCPCS code J3490. Added HCPCS code J3590.
10/22/19	Coding updated, added HCPCS code J0593 (new code effective 10/1/19), removed HCPCS code J3590.
12/01/20	Annual Review, approved November 19, 2020. Updated Haegarda (pdC1-INH) coverage criteria to patients ≥6 years of age.
02/01/21	Interim Review, approved January 12, 2021. Added coverage criteria for Orladeyo (berotralstat) for prophylaxis of acute angioedema attacks in patients 12 years and older. Criteria for Orladeyo are effective February 1, 2021. Updated Berinert (pdC1-

Date	Comments
	INH) criteria adding coverage for acquired angioedema. Updated Cinryze (pdC1-INH) criteria adding patient age, limits to danazol use, and acute HAE frequency requirements. Updated Firazyr (icatibant) criteria to require use of generic icatibant first. Updated Haegarda (pdC1-INH) criteria adding limits to danazol use and acute HAE frequency requirements. Updated Ruconest (rhC1-INH) criteria to patients 13 and older. Updated Takhzyro (lanadelumab-flyo) criteria adding limits to danazol use, acute HAE frequency requirements, and quantity limit. Updated criteria for Berinert, Cinryze, Firazyr, Haegarda, Ruconest, and Takhzyro become effective on May 6, 2021, following 90-day provider notification.
11/01/21	Annual Review, approved October 21, 2021. Added site of service review for Cinryze (pdC1-INH) for dates of service on or after February 4, 2022.
11/01/22	Annual Review, approved October 24, 2022. Added a new generic product called Sajazir (icatibant) with the identical coverage criteria as generic icatibant. Added generic Sajazir as a qualifying drug an individual must try prior to brand Firazyr (icatibant). Added Sajazir as a qualifying acute treatment drug within criteria for Cinryze, Haegarda, Orladeyo, and Takhzyro. Changed the wording from "patient" to "individual" throughout the policy for standardization.
05/01/23	Annual Review, approved April 24, 2023. Reviewed prescribing information for all drugs listed in policy and reviewed product availability. Updated Takhzyro coverage criteria from individuals 12 years of age and older to individuals 2 years of age and older.
09/01/24	Annual Review, approved August 13, 2024. Removed requirement to try Danocrine (danazol) or another androgen for adult males from Haegarda (pdC1-INH), Orladeyo (berotralstat), Takhzyro (lanadelumab), and Cinrzye (pdC1-INH). The following policy change is effective December 5, 2024, following 90-day provider notification. Updated Berinert (pDC1-INH), Kalbitor (ecallantide), and Ruconest (rhC1-INH) to require trial with generic icatibant or Sajazir (icatibant).
02/01/25	Annual Review, approved January 27, 2025. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members; only Medical Necessity criteria for the infusion drug applies pursuant to Alaska HB 226 (link added). Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS).
07/01/25	Interim Review, approved June 10, 2025. Removed Sajazir (icatibant) as a preferred treatment for acute attacks of hereditary angioedema. Updated Berinert (pdC1-INH), Firazyr (icatibant), Kalbitor (ecallantide), and Ruconest (rhC1-INH) coverage criteria to clarify that the generic icatibant step therapy requirement applies to individuals aged 18 years or older who are not currently pregnant.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.