Introduction

Hereditary angioedema (HAE) is an inherited condition. Patients 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 or less severe in different patients.

The unpredictability of these attacks is a serious problem. About half of patients with HAE will have at least one attack with life threatening throat swelling at some point in their lives. A recent survey of 457 patients 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 the 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.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Berinert® (pdC1-INH) IV** | **Berinert® (pdC1-INH) may be considered medically necessary for treatment of acute attacks of angioedema in:**  
- Patients 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**  
- Patients 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**  
- Patient has two 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**  
- Treatment is not used concomitantly with other targeted HAE-specific therapies for acute treatment  

*Low is below the lower limit of normal as defined by the laboratory test.*

| **Cinryze® (pdC1-INH) IV** | **Cinryze® (pdC1-INH) may be considered medically necessary for the long-term prophylaxis of acute angioedema attacks in:**  
- Patients 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**  

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
|      | Patients 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**  
|      | Patient has two 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**  
|      | Prior treatment with Danocrine® (danazol) or another androgen has been ineffective, not tolerated, or contraindicated  
|      | **AND**  
|      | Treatment is not used concomitantly with other targeted HAE-specific therapies for prophylactic treatment  

*Low is below the lower limit of normal as defined by the laboratory test.

**Firazyr® (icatibant) SC, generic icatibant**  
**Firazyr® (icatibant) and generic icatibant may be considered medically necessary for treatment of acute attacks of angioedema in:**  
**Patients ≥ 18 years of age**  
**AND**  
**Patients 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**  
**Patients with type II HAE established by ALL the following documented laboratory values:**  
- *Low C4 levels  
- Normal or high C1-INH protein (antigenic) levels
Drug | Medical Necessity
--- | ---
 | • *Low C1-INH functional levels
 OR
 • Patients 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
 • Patient has two 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

*Low is below the lower limit of normal as defined by the laboratory test.

<table>
<thead>
<tr>
<th>Haegarda® (pdC1-INH) SC</th>
<th>Haegarda® (pdC1-INH) may be considered medically necessary for the long-term prophylaxis of acute angioedema attacks in:</th>
</tr>
</thead>
</table>
| | • Patients ≥12 years of age
 AND
 • Patients 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
 • Patients 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 |
### Drug Medical Necessity

**AND**
- Patient has two 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**
- Prior treatment with Danocrine® (danazol) or another androgen has been ineffective, not tolerated, or contraindicated

**AND**
- Treatment is not used concomitantly with other targeted HAE-specific therapies for prophylactic treatment

*Low is below the lower limit of normal as defined by the laboratory test.

**Kalbitor® (ecallantide) SC**

**Kalbitor® (ecallantide) may be considered medically necessary for treatment of acute attacks of angioedema in:**
- Patients ≥12 years of age

**AND**
- Patients 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**
- Patients 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**
- Patients with acquired angioedema established by ALL the following documented laboratory values:
  - *Low complement component 1q (C1q) levels
  - *Low C4 levels
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
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<tbody>
<tr>
<td></td>
<td>o  *Low C1-INH protein (antigenic) levels</td>
</tr>
<tr>
<td></td>
<td>o  *Low C1-INH functional levels</td>
</tr>
<tr>
<td>AND</td>
<td>Patient has two or more of the following clinical features:</td>
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<td>o  Recurrent angioedema without wheals or urticaria</td>
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<td>o  Recurrent abdominal attacks</td>
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<td></td>
<td>o  Positive family history for type I HAE or type II HAE</td>
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<tr>
<td></td>
<td>o  Failure to respond to antihistamines, glucocorticoids or epinephrine</td>
</tr>
<tr>
<td>AND</td>
<td>Treatment is to be administered by a healthcare professional with appropriate medical support to manage anaphylaxis</td>
</tr>
<tr>
<td>AND</td>
<td>Treatment is not used concomitantly with other targeted HAE-specific therapies for acute treatment</td>
</tr>
</tbody>
</table>

*Rlow is below the lower limit of normal as defined by the laboratory test.

<table>
<thead>
<tr>
<th>Ruconest® (rhC1-INH) IV</th>
<th>Ruconest® (rhC1-INH) may be considered medically necessary for treatment of acute attacks of angioedema in:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients ≥ 11 years of age</td>
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<tr>
<td>AND</td>
<td>Patients with type I hereditary angioedema (HAE) established by ALL the following documented laboratory values:</td>
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<tr>
<td></td>
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<td></td>
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<td>Drug</td>
<td>Medical Necessity</td>
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<tr>
<td>------</td>
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</tr>
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<td></td>
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<td></td>
<td><strong>AND</strong></td>
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</tr>
<tr>
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<td></td>
</tr>
</tbody>
</table>

**Takhyzro® (lanadelumab-flyo) SC**  

*Takhyzro® (lanadelumab-flyo) may be considered medically necessary for the long-term prophylaxis of acute angioedema attacks in:*  

• Patients ≥12 years of age  

**AND**  

• Patients with type I hereditary angioedema (HAE) established by ALL the following documented laboratory values:  
  o *Low complement component 4 (C4) levels  
  o *Low C1 esterase inhibitor (C1-INH) protein (antigenic) levels  

**OR**  

• Patients with type II HAE established by ALL the following documented laboratory values:  
  o *Low C4 levels  
  o Normal or high C1-INH protein (antigenic) levels  
  o *Low C1-INH functional levels  

**AND**  

• Patient has two or more of the following clinical features:  
  o Recurrent angioedema without wheals or urticaria  
  o Recurrent abdominal attacks  
  o Positive family history  
  o Failure to respond to antihistamines, glucocorticoids or epinephrine  

**AND**  

• Prior treatment with Danocrine® (danazol) or another androgen has been ineffective, not tolerated, or contraindicated  

**AND**
Drug Medical Necessity

- Treatment is not used concomitantly with other targeted HAE-specific therapies for prophylactic treatment

*Low is below the lower limit of normal as defined by the laboratory test.

Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Approval</td>
<td>Initial approval for 3 months requires all of the following criteria listed by drug above be met.</td>
</tr>
<tr>
<td>Reauthorization</td>
<td>Continued therapy will be approved for periods of one year as long as the above conditions are met, and the patient has shown and continues to show a reduction in baseline frequency of attacks (LTP), or duration and severity of attacks (acute treatment).</td>
</tr>
</tbody>
</table>

Documentation Requirements

The patient’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
- Applicable laboratory testing results

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS</td>
<td></td>
</tr>
<tr>
<td>J0593</td>
<td>Injection, lanadelumab-flyo (Taklyzo®), 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) (new code effective 10/1/19)</td>
</tr>
<tr>
<td>J0596</td>
<td>Injection, C1 esterase inhibitor (recombinant), Ruconest, 10 units</td>
</tr>
<tr>
<td>J0597</td>
<td>Injection, C-1 esterase inhibitor (human), Berinert, 10 units</td>
</tr>
</tbody>
</table>
### Related Information

**Consideration of Age**

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

**Benefit Application**

Berinert® (pdC1-INH), Cinryze® (pdC1-INH), Firazyry® (icatibant) and generic icatibant, Haegarda® (pdC1-INH), Kalbitor® (ecallantide), Ruconest® (rhC1-INH), and Takhyzro® (lanadelumab-flyo) are managed through both the Pharmacy and 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 patients. 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 patients 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 patients. In a recent survey of 457 patients 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 patient were $25,884 and $16,108, respectively, in 2007 US dollars. 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 Xla in the intrinsic coagulation cascade.

HAE patients have low levels of endogenous or functional C1 esterase inhibitor. Although the events that induce attacks of angioedema in HAE patients 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 (ie, antihistamines, epinephrine, and corticosteroids) because these treatments target mast-cell mediated sequelae (ie, 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 (eg, surgery or dental procedures), and on-demand treatment of acute attacks. Androgenic steroids were the only drug class approved for use for this condition in the US until a decade ago. Danocrine (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. Oxymetholone (ANADROL), oxandrolone (OXANDRIN), and methyltestosterone have been used off-label for long-term HAE attack prophylaxis.

Over the last decade, seven 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 ecallantide (KALBITOR), an inhibitor of human plasma kallikrein, was approved for the treatment of acute attacks of HAE. In 2011, icatibant (FIRAZYR), 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 patients 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 patients 12 years and older.

**Preferred Existing Therapy**

Consensus US and international guidelines recommend all patients with HAE have access to an effective on-demand HAE-specific agent. Currently these include IV plasma-derived C1-INH
(CINRYZE, BERINERT), recombinant C1-INH (RUCONEST), ecallantide (KALBITOR), and icatibant (FIRAZYR).

For short-term/procedural prophylaxis the consensus US guidelines recommend C1-INH, FFP, or short-term high-dose anabolic steroids. For long-term prophylaxis they recommend anabolic steroids (eg, danocrine, OXANDRIN, methyltestosterone) or C1-INH over antifibrinolytics (ie, aminocaproic acid or tranexamic acid). However, anabolic steroids are contraindicated in pregnancy, and relatively contraindicated in children and those with hepatic dysfunction.

The cornerstone of treatment for angioedema attacks secondary to angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) therapy is discontinuation of the offending agent.

**Other Therapeutic Alternatives**

The consensus US guidelines list FFP as a second-line therapeutic alternative to on-demand therapy with an HAE-specific agent. FFP is considered a second-line alternative because 1) it may acutely exacerbate some attacks and 2) the risk of blood-borne illnesses (eg, viruses). Some attacks may also be managed symptomatically only (based on region of the body involved and swelling). Antifibrinolytics and androgens are not recommended for treatment of bradykinin-mediated acute attacks of angioedema.

For long-term prophylaxis, antifibrinolytics are considered a second-line therapeutic alternative because they are less effective than androgen therapy and C1-INH.

**Table 1. Comparison of Targeted HAE-specific Treatments**

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA-approved Indication</th>
<th>Mechanism of Action</th>
<th>Dose / Route</th>
<th>Time to Onset of Relief (Duration)</th>
<th>Serious Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berinert</td>
<td>Acute abdominal, facial, or laryngeal attacks (no lower age limit)</td>
<td>pdC1-INH replacement</td>
<td><strong>On demand</strong>: 20 U/kg IV (1500 U) <em>Prophylaxis</em>: 10-30 U/kg IV pre-procedure or 1-2 times/week (1500 units BIW)</td>
<td>Median: 0.8 hrs (22 hrs)</td>
<td>Rare: anaphylaxis, thrombosis Theoretical: blood-borne infections</td>
</tr>
<tr>
<td>Drug</td>
<td>FDA-approved Indication</td>
<td>Mechanism of Action</td>
<td>Dose / Route</td>
<td>Time to Onset of Relief (Duration)</td>
<td>Serious Adverse Effects</td>
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</tr>
<tr>
<td>Ruconest</td>
<td>Acute HAE attacks in patients ≥11 yrs of age</td>
<td>rhC1-INH replacement</td>
<td>On demand: 50 U/kg IV (4200 U) *Prophylaxis: N/A</td>
<td>Median: 1.5 hrs (10 hrs)</td>
<td>Rare: hypersensitivity (rabbit-sensitized)</td>
</tr>
<tr>
<td>Cinryze</td>
<td>Prophylaxis of HAE attacks in patients ≥11 yrs of age</td>
<td>pdC1-INH replacement</td>
<td>*On-demand: 1000 U IV, if needed repeat x 1 after 1 hr *Prophylaxis: 1000 U IV BIW</td>
<td>Median: 0.5 hrs (56 hrs)</td>
<td>Rare: anaphylaxis, thrombosis Theoretical: blood-borne infections</td>
</tr>
<tr>
<td>Haegarda</td>
<td>Prophylaxis of HAE attacks in patients ≥12 yrs of age</td>
<td>pdC1-INH replacement</td>
<td>*On-demand: N/A *Prophylaxis: 60 IU/kg SC BIW</td>
<td>Median: N/A (N/A)</td>
<td>Rare: hypersensitivity Theoretical: thrombosis, blood-borne infections</td>
</tr>
<tr>
<td>Kalbitor</td>
<td>Acute HAE attacks in patients ≥12 yrs of age</td>
<td>Plasma kallikrein inhibitor</td>
<td>On-demand: 30 mg SC *Prophylaxis: N/A</td>
<td>Median: 1 hr (4-10 hrs)</td>
<td>Uncommon: anaphylaxis, development of anti-C1-INH antibodies (must be administered by a health professional)</td>
</tr>
<tr>
<td>Takhyzro</td>
<td>Prophylaxis of HAE attacks in patients ≥12 yrs of age</td>
<td>Plasma kallikrein inhibitor</td>
<td>*On-demand: N/A *Prophylaxis: 300 mg SC Q2W</td>
<td>Median: N/A (N/A)</td>
<td>N/A</td>
</tr>
<tr>
<td>Firazyr</td>
<td>Acute HAE attacks in patients ≥18 yrs of age</td>
<td>Bradykinin-2 receptor antagonist</td>
<td>On-demand: 30 mg SC *Prophylaxis: N/A</td>
<td>Median: 2 hrs (6 hrs)</td>
<td>Theoretical: Worsening of an ongoing ischemic event</td>
</tr>
</tbody>
</table>

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 patients ≥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 patients 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. The majority of 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.


18. Haegarda® (C1 esterase inhibitor [subcutaneous]) prescribing information. CSL Behring; Kankakee, IL. June 2017.

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/01/18</td>
<td>New policy, approved October 9, 2018, effective February 1, 2019. Added codes J0596, J0597, J0598, J1290, J1744, and J3490.</td>
</tr>
<tr>
<td>12/20/18</td>
<td>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.</td>
</tr>
<tr>
<td>02/01/19</td>
<td>Contents from policy 5.01.594 moved back to this policy. Added HCPCS code J0599.</td>
</tr>
<tr>
<td>04/01/19</td>
<td>Interim Review, approved March 19, 2019. Updated criteria for Cinryze, Firazyr, Haegarda, Kalbitor and Takhyzo.</td>
</tr>
<tr>
<td>08/01/19</td>
<td>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.</td>
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<tr>
<td>10/22/19</td>
<td>Coding updated, added HCPCS code J0593 (new code effective 10/1/19), removed HCPCS code J3590.</td>
</tr>
</tbody>
</table>

**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. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

**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.
Discrimination Is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
• Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  • Qualified sign language interpreters
  • Written information in other formats (large print, audio, accessible electronic formats, other formats)
• Provides free language services to people whose primary language is not English, such as:
  • Qualified interpreters
  • Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filling a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Amharic):

 Ethiopian (Amharic):

 العربية (Arabic):

Oromo (Cushite):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):

Iloko (Ilocano):

Italiano (Italian):

037338 (07-2016)
Japanese (Japanese):
この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれている場合があります。この通知には記載されている情報が重要な日々をご確認ください。健康保険や無料サービスを維持するには、特定の期日までに行動を取られなければなりません。ご自身の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

Korean (Korean):
본 통지서에는 중요한 정보가 들어있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross를 통한 커버리지를 위한 정보를 제공하고 있습니다. 본 통지서에는 특허이 되는 및 피해자들이 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 것입니다.
귀하는 이러한 정보와 도움을 귀하의 안면 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)로 전화해보십시오.

Polish (Polish):

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e em custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Romanian (Romanian):

Russian (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Spanish (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claves en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

Thai (Thai):
ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้มีข้อมูลสำคัญเกี่ยวกับการพิจารณาการขอรับและประกันสุขภาพของคุณ Premera Blue Cross และการเข้าสู่การประกันในกรณีที่คุณจะต้อง ดำเนินการในกําลังการเป็นไปตามที่ระบุไว้ในประกาศนี้จะมีการประกันสุขภาพของคุณหรือการช่วยเหลือที่ มีมีข้อมูลที่คุณต้องการที่จะรับรู้และทำความเข้าใจในการประกันและไม่มีการพิจารณาอะไร โทร 800-722-1471 (TTY: 800-842-5357).

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані в цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити відповідні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):