PREMERA | BLUE CROSS

PHARMACY / MEDICAL POLICY – 5.01.587

Hereditary Angioedema

Effective Date:	Feb. 1, 2021*	RELATED MEDICAL POLICIES:
Last Revised:	Jan 12, 2021	None
Replaces:	N/A	
***This policy has been updated. View changes.**		

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

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.

Policy Coverage Criteria

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:
	• 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
	
	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) 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

Drug	Medical Necessity
	○ *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** • 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 **Note:** *Low is below the lower limit of normal as defined by the laboratory test.
Icatibant, generic **Managed under Pharmacy and Medical benefit**	**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:

Drug	Medical Necessity
	○ *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 ○ *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 **Note:** *Low is below the lower limit of normal as defined by the laboratory test.
Firazyr® (icatibant) SC **Managed under Pharmacy and Medical benefit**	**Firazyr® (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** • The patient 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 **Managed under Pharmacy and Medical benefit**	**Haegarda® (pdC1-INH) may be considered medically necessary for the long-term prophylaxis of acute angioedema attacks in:** • Patients ≥6 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:

Drug	Medical Necessity
	○ *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 **Note:** *Low is below the lower limit of normal as defined by the laboratory test.
Kalbitor® (ecallantide) SC **Managed under Pharmacy and Medical benefit**	**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**

Drug	Medical Necessity

	• 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 to be administered by a healthcare professional with appropriate medical support to manage anaphylaxis
	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.

Orladeyo® (berotralstat) oral
 	
Managed under Pharmacy benefit
	Orladeyo® (berotralstat) 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:
	  ○ *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 **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** • For males 18 years of age or older prior treatment with Danocrine® (danazol) or another androgen has been ineffective, not tolerated, or contraindicated **AND** • One 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®, or Ruconest® **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 **AND** • Dose prescribed is ≤ 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:** • Patients ≥ 11 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

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

Length of Approval	
Approval	**Criteria**
Initial authorization	**All drugs listed in policy may be approved up to 3 months.**
Reauthorization criteria	**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 for long-term prophylaxis drugs or duration and severity of attacks for acute treatment drugs.**

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 **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® 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.

Benefit Application

Orladeyo® (berotralstat) is managed through the Pharmacy benefit. Firazyr® (icatibant), generic icatibant, Haegarda® (pdC1-INH), Kalbitor® (ecallantide), 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 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.[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 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

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 recommends that HAE attacks are treated with either C1-INH, ecallantide, or icatibant.

For short-term/procedural prophylaxis the WAO/EAACI guidelines recommend short-term prophylaxis before procedures that can induce an attack. For long-term prophylaxis they recommend use of C1-INH 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 for the treatment of HAE attacks in children under the age of 12.

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 ≥11 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 ≥11 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 ≥12 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
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	*On-demand: N/A	Median: N/A	N/A

Drug	FDA-approved Indication	Mechanism of Action	Dose / Route	Time to Onset of Relief (Duration)	Serious Adverse Effects
		kallikrein inhibitor	Prophylaxis: 300 mg SC Q2W	(N/A)	
Firazyr	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 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.

2020 Update

Reviewed prescribing information for all drugs listed in policy. Haegarda® (pdC1-INH) prescribing information was updated from patients ≥12 years of age to patients ≥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.

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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.

Date	Comments
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.

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.

PREMERA | BLUE CROSS

An Independent Licensee of the Blue Cross Blue Shield Association

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 with:
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 filing 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 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html.

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).

አማሪኛ (Amharic):
ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀኖች ሊኖሩ ይችላሉ። የጤናን ሽፋንዎን ለመጠበቅና በአከፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና ያለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መብት አለዎት።በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):
يحوي هذا الإشعار معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تريد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تواريخ معينة للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):
Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

Français (French):
Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devrez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resevwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):
Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

Hmoob (Hmong):
Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnub tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti apliksayonyo wenno coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

日本語 (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。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望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。

한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하는 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

ລາວ (Lao):
ແຈ້ງການນີ້ມີຂໍ້ມູນສຳຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສຳຄັນກ່ຽວກັບຄຳຮ້ອງສະໝັກ ຫຼື ຄວາມຄຸ້ມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີສຳຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈຳເປັນຕ້ອງດຳເນີນການຕາມກຳນົດເວລາສະເພາະເພື່ອຮັກສາຄວາມຄຸ້ມຄອງປະກັນສຸຂະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເລື່ອງຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄວ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໂທຫາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):
សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរ៉ាប់រងរបស់អ្នកតាមរយៈ Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ចេញសមត្ថភាព ដល់កំណត់ថ្ងៃជាក់ច្បាស់នានា ដើម្បីនឹងរក្សាទុកការជានាវ៉ាប់រងសុខភាពរបស់អ្នក ឬប្រាក់ជំនួយចេញផ្លែ។ អ្នកមានសិទ្ធិទទួលព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):
ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਜਿਸ ਜਵਚ ਖਾਸ ਤਾਰੀਖਾ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀ ਜਸਹਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ਼ ਤੋਂ ਪਹਿਲਾਂ ਕੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫ਼ਤ ਵਿੱਚ ਤੇ ਆਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):
این اعلامیه حاوی اطلاعات مهم میباشد .این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید .شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید .شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کاربران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócic uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

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 sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):
Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastre de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența privitoare la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (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).

Fa'asamoa (Samoan):
Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'amatalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (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 clave 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):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaaring naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):
ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย 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 у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні 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. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):
Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).