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Subject: Hereditary Angioedema Drug Therapy

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Position Statement | Billing/Coding | Reimbursement | Program Exceptions | Definitions | Related Guidelines

Other | References | Update

DESCRIPTION:

Hereditary angioedema (HAE) is characterized by self-limited tissue swelling that most often affects the skin and upper respiratory and gastrointestinal tracts. The prevalence of HAE is estimated between 1 in 10,000 to 1 in 150,000 worldwide, and the estimated population of people with HAE in the United States ranges from 6,000 to 10,000 people. There is a significant age-related difference in frequency of HAE attacks (there is an increase at the time of puberty), but quality of life is affected significantly at all ages. The underlying cause of HAE is attributed to autosomal-dominant inheritance of mutations in the C1-inhibitor (C1-INH) gene, which was mapped to chromosome 11. More than 200 mutations of this gene have been linked to the clinical HAE manifestations.

The majority of HAE cases show a familial pattern of inheritance, whereas 25% are related to spontaneous mutations. There are three types of HAE; two types of HAE account for the majority of cases. An estimated 85% of all cases are type 1 HAE, which is characterized by a low levels of normal C1-INH. The majority of individuals with non-type 1 HAE have type 2 HAE, characterized by normal or elevated levels of C1-INH but it doesn't function properly. Type III HAE is extremely rare, is an estrogen dependent form of angioedema, and occurs predominantly in females.

The initial laboratory test includes two specific blood tests to confirm the diagnosis of HAE: 1) the level of C1-INH and whether it is functioning properly and 2) C2 and C4, which will usually reveal low levels even when an attack is not ongoing. Table 1 describes the expected results for the blood tests. Indications for testing include any of the following: recurrent angioedema, laryngeal edema, abdominal pain in the absence of urticaria, or a family history of HAE.

Table 1

Blood tests for different types of angioedema			
HAE Type	**C1-INH antigen**	**C1-INH function**	**C4**
Type I	Low	Low	Low
Type II	Normal to elevated	Low	Low
Type III	Normal	Normal	Normal

Treatment options for HAE types I and II vary in terms of treatment for acute attacks, chronic therapy for individuals with frequent attacks, and short-term prophylactic treatment before or during a known exposure to triggers such as infection, surgery, dental work, and trauma. According to the current 2010 international consensus algorithm for the diagnosis, therapy, and management of HAE, supportive

therapy combined with specific therapies is the preferred therapy for HAE attacks. General measures for treating attacks involve hydration, pain relief, and treating as soon as possible with plasma-derived C1-INH (i.e., Berinert®), ecallantide (Kalbitor®), icatibant (Firazyr®), sebetralstat (Ekterly™), and recombinant C1-INH (Ruconest®). For individuals with frequent episodes of angioedema or severe HAE, preventive measures include attenuated androgens (e.g., danazol), antifibrinolytic agents, berotralstat (Orladeyo), garadacimab-gxii (Andembry™), lanadelumab-flyo (Takhzyro™), or C1-INH (i.e., Cinryze®, Haegarda®).

Currently there are four commercially available C1 inhibitors available in the United States. Cinryze and Haegarda are approved by the US Food and Drug Administration (FDA) for prophylaxis in adolescents and adults; however, have not been approved for the treatment of acute attacks. In contrast, Berinert and Ruconest are approved for use in acute attacks. The other treatment options, ecallantide and icatibant, work as kinin-pathway modulators. Ecallantide is a recombinant protein that acts as a potent reversible inhibitor of plasma kallikrein that ultimately stops production of bradykinin and the edema progression in acute HAE attacks. The main adverse event is the possibility of anaphylaxis, which can occur in up to 3% of individuals treated with subcutaneous ecallantide. To ensure that the benefits of this product outweigh the risks, the FDA requires a risk evaluation and mitigation strategy (REMS) for this agent. Self-treatment at home is strongly discouraged. Icatibant is a synthetic decapeptide that is a specific and selective competitive antagonist of the bradykinin B2 receptor (BK2R). It is structurally similar to bradykinin and binds to the BK2R with high affinity. Similar to ecallantide, icatibant is indicated for the treatment of acute angioedema in individuals with HAE.

Type III HAE is a relatively new disorder. At this time, a diagnostic test to confirm type III HAE is unavailable and the pathogenic mechanism(s) by which swelling is produced are uncertain. Appropriate treatment modalities have not been determined. The evidence supporting treatment with C1 inhibitors and other treatment options (e.g., ecallantide, icatibant) is limited to observational data (e.g., case reports and case series). There is no consensus as to appropriate treatment of type III HAE (i.e., those with recurrent angioedema characterized by normal C1 inhibitor levels).

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, or emergency facility is not considered medically necessary.

NOTE: Andembry, Haegarda, and Orladeyo are the preferred products for prophylaxis of HAE attacks. Generic icatibant is the preferred product for treatment of an acute HAE attack.

Initiation and continuation of hereditary angioedema (HAE) drug therapy **meets the definition of medical necessity** when ALL of the following criteria are met:

1. HAE drug therapy is prescribed by a board certified allergist or immunologist
2. Member is diagnosed with HAE as evidenced by **BOTH** of the following:
    a. C4 level is below laboratory's lower limit of normal – laboratory documentation must be provided
    b. C1-inhibitor (C1-INH) level meets **ONE** of the following:
        i. C1-INH antigen level is below laboratory's lower limit of normal – laboratory documentation must be provided
        ii. C1-INH functional level is less than 50% of laboratory's lower limit of normal – laboratory documentation must be provided

iii. Presence of known HAE-causing C1-INH mutation – laboratory documentation must be provided (Accepted for Adembry, Cinryze, Dawnzera, Haegarda, Orladeyo, and Takhzyro ONLY)

3. **ONE** of the following:
    a. Member is not receiving a medication known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) – current (within the past three months) medication list must be provided
    b. Member is receiving a medication known to cause angioedema and continued use is appropriate – detailed explanation of clinical rationale for continued use must be provided
4. **ONE** of the following:
    a. Request is for initiation of HAE drug therapy and member will maintain a treatment log documenting all HAE attacks and required treatment – a copy of the treatment log must be submitted upon continuation of HAE drug therapy or if quantity limits are exceeded
    b. Request is for continuation of HAE drug therapy that has not been previously approved by Florida Blue and the member will maintain a treatment log documenting all HAE attacks and required treatment – a copy of the treatment log must be submitted submitted upon continuation of HAE drug therapy or if quantity limits are exceeded
    c. Request is for continuation of HAE drug therapy previously approved by Florida Blue and the member has maintained a treatment log documenting all HAE attacks and required treatment – a copy of the treatment log with at least 180 days of documentation must be submitted
5. Member meets product specific criteria outlined in Table 2

Table 2

Table 2. Criteria for use of hereditary angioedema (HAE) drug therapy

Product	Criteria
Products for Prophylaxis of HAE	
Berotralstat *Orladeyo.* *Orladeyo Pellets*	Initiation and continuation **meet the definition of medical necessity** when **ALL** of the following criteria are met: 1. Indication for use is prophylaxis of hereditary angioedema (HAE) 2. Member is 2 years of age or older 3. Member has a history of 2 or more HAE attacks per month 4. Oladeyo is not used concomitantly with Andembry, Cinryze, Dawnzera, Haegarda, or Takhzyro 5. Dose does not exceed: a. Age 12 years and older: 150 mg once daily b. Age 2 years to less than 12 years: 132 mg once daily (oral pellets) 6. Dispensed quantity does not exceed 30 capsules or unit-dose pellet packets per 30 days Duration of approval: 180 days
Donidalorsen *Dawnzera*	Initiation and continuation meet the definition of medical necessity when ALL of the following criteria are met: 1. Indication for use is prophylaxis of hereditary angioedema (HAE) 2. Member is 12 years of age or older

	3. Member has a history of 2 or more HAE attacks per month 4. Initiation requests only: a. Member has had an inadequate response (defined as HAE attack requiring acute treatment), FDA labeled contraindication, or intolerance to treatment with ALL of the following – documentation from the medical record of the inadequate response, specific FDA labeled contraindication, or clinically meaningful intolerance to each product must be provided: i. Andemby ii. Cinryze iii. Haegarda iv. Orladeyo v. Takhzyro 5. Dawnzera is not used concomitantly with Andembry, Cinryze, Haegarda, Orladeyo, or Takhzyro 6. Dose does not exceed: a. Initiation: 80 mg every 4 weeks for 6 months b. Continuation: i. Member has remained attack free during treatment initiation: 80 mg every 8 weeks ii. Member experienced an HAE attack requiring acute treatment (as evidenced by submitted treatment log) during treatment initiation: 80 mg every 4 weeks iii. Member experienced an HAE attack requiring acute treatment (as evidenced by submitted treatment log) while receiving 80 mg every 8 weeks: 80 mg every 4 weeks 7. Dispensed quantity does not exceed: a. Initiation: 1 autoinjector per 28 days b. Continuation: i. Member has remained attack free during treatment initiation: 1 autoinjector per 56 days ii. Member experienced an HAE attack requiring acute treatment (as evidenced by submitted treatment log) during treatment initiation: 1 autoinjector per 28 days iii. Member experienced an HAE attack requiring acute treatment (as evidenced by submitted treatment log) while receiving 80 mg every 4 weeks: 1 autoinjector per 28 days Duration of approval: 180 days
Garadacimab-gxii *Andembry*	Initiation and continuation **meet the definition of medical necessity** when **ALL** of the following criteria are met: 1. Indication for use is prophylaxis of hereditary angioedema (HAE) 2. Member is 12 years of age or older 3. Member has a history of 2 or more HAE attacks per month 4. Andembry is not used concomitantly with Cinryze, Dawnzera, Haegarda, Orladeyo, or Takhzyro 5. Dose does not exceed: a. Loading dose: 400 mg SQ on day 1

	b. Maintenance dose: 200 mg SQ every month 6. Dispensed quantity does not exceed 2 syringes on month 1, then 1 syringe per 30 days every month thereafter Duration of approval: 180 days
Human C1 Inhibitor *Cinryze*	Initiation and continuation meet the definition of medical necessity when ALL of the following criteria are met: 1. Indication for use is prophylaxis of hereditary angioedema (HAE) 2. Member is 6 years of age or older 3. Member has a history of 2 or more HAE attacks per month 4. Initiation requests only: c. Member has had an inadequate response (defined as HAE attack requiring acute treatment), FDA labeled contraindication, or intolerance to treatment with ALL of the following – documentation from the medical record of the inadequate response, specific FDA labeled contraindication, or clinically meaningful intolerance to each product must be provided: i. Andemby ii. Haegarda iii. Orladeyo a. 5. Cinryze is not used concomitantly with Andembry, Dawnzera, Haegarda, Orladeyo, or Takhzyro 6. Dose does not exceed 1,000 units (10 mL) every 3 to 4 days 7. Dispensed quantity does not exceed 10,000 units (20 vials) per 30 days Duration of approval: 180 days
Human C1 Inhibitor *Haegarda*	Initiation and continuation meet the definition of medical necessity when ALL of the following criteria are met: 1. Indication for use is prophylaxis of hereditary angioedema (HAE) 2. Member is 6 years of age or older 3. Member has a history of 2 or more HAE attacks per month 4. Haegarda is not used concomitantly with Andembry, Cinryze, Dawnzera, Orladeyo, or Takhzyro 5. Dose does not exceed 60 IU/kg twice weekly 6. Dispensed quantity does not exceed 16 vials per 30 days Duration of approval: 180 days
Lanadelumab -flyo *Takhzyro*	Initiation and continuation meet the definition of medical necessity when ALL of the following criteria are met: 1. Indication for use is prophylaxis of hereditary angioedema (HAE) 2. Member is 12 years of age or older 3. Member has a history of 2 or more HAE attacks per month 4. Initiation requests only: d. Member has had an inadequate response (defined as HAE attack requiring acute treatment), FDA labeled contraindication, or intolerance to treatment with ALL of the following – documentation from the medical record of the inadequate response, specific FDA

	labeled contraindication, or clinically meaningful intolerance to each product must be provided: i. Andemby ii. Haegarda iii. Orladeyo 5. Takhzyro is not used concomitantly with Andembry, Cinryze, Dawnzera, Haegarda, or Orladeyo 6. Dose does not exceed: a. Initiation: 300 mg every 2 weeks for 6 months b. Continuation: i. Member has remained attack free during treatment initiation: 300 mg every 4 weeks ii. Member experienced an HAE attack requiring acute treatment (as evidenced by submitted treatment log) during treatment initiation: 300 mg every 2 weeks iii. Member experienced an HAE attack requiring acute treatment (as evidenced by submitted treatment log) while receiving 300 mg every 4 weeks: 300 mg every 2 weeks 7. Dispensed quantity does not exceed: a. Initiation: 2 vials per 28 days b. Continuation: i. Member has remained attack free during treatment initiation: 1 vial per 28 days ii. Member experienced an HAE attack requiring acute treatment (as evidenced by submitted treatment log) during treatment initiation: 2 vials per 28 days iii. Member experienced an HAE attack requiring acute treatment (as evidenced by submitted treatment log) while receiving 300 mg every 4 weeks: 2 vials per 28 days Duration of approval: 180 days
Products for Acute Angioedma Attack of HAE	
Human C1 Inhibitor *Berinert*	Initiation and continuation meet the definition of medical necessity when ALL of the following criteria are met: 1. Indication for use is treatment of acute angioedema attack (e.g., abdominal, facial, laryngeal) of hereditary angioedema (HAE) 2. Initiation requests only: a. Member has had an inadequate response (defined as an HAE attack unresponsive to treatment with generic icatibant), FDA labeled contraindication, or intolerance to treatment with generic icatibant – documentation from the medical record must be provided 3. Human C1 inhibitor (Berinert) is not used concomitantly with ecallantide (Kalbitor), icatibant (Firazyr), recombinant C1 inhibitor (Ruconest), or sebetralstat (Ekterly) 4. Dose does not exceed 20 units/kg 5. Dispensed quantity does not exceed 8,000 units (16 vials) per 30 days [a] Duration of approval: 180 days

Ecallantide *Kalbitor*	Initiation and continuation meet the definition of medical necessity when ALL of the following criteria are met: 1. Indication for use is treatment of acute angioedema attack (e.g., abdominal, facial, laryngeal) of hereditary angioedema (HAE) 2. Member is 12 years of age or older 3. Initiation requests only: a. Member has had an inadequate response (defined as an HAE attack unresponsive to treatment with generic icatibant), FDA labeled contraindication, or intolerance to treatment with generic icatibant – documentation from the medical record must be provided 4. Ecallantide (Kalbitor) is not used concomitantly with Berinert, icatibant (Firazyr), recombinant C1 inhibitor (Ruconest), or sebetralstat (Ekterly) 5. Dose does not exceed 30 mg (3 mL) 6. Dispensed quantity does not exceed 120 units (12 vials) per 30 days [a] Duration of approval: 180 days
Icatibant *Firazyr*	Initiation and continuation meet the definition of medical necessity when ALL of the following criteria are met: 1. Indication for use is treatment of acute angioedema attack (e.g., abdominal, facial, laryngeal) of hereditary angioedema (HAE) 2. Member is 18 years of age or older 3. Icatibant (Firazyr) is not used concomitantly with Berinert, ecallantide (Kalbitor), recombinant C1 inhibitor (Ruconest), or sebetralstat (Ekterly) 4. Dose does not exceed 30 mg (3 mL) every 6 hours up to 90 mg (9 mL) in 24 hours 5. Dispensed quantity does not exceed 360 mg (12 syringes) per 30 days[a] 6. **For brand Firazyr only**: a. Member has tried and had intolerable adverse effects to generic icatibant – specific intolerance to generic icatibant and rationale for use of brand Firazyr must be provided in addition to **BOTH** of the following: i. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safetyinformation/forms-reporting-fda ii. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf Duration of approval: 180 days
Recombinant C1 Inhibitor *Ruconest*	Initiation and continuation meet the definition of medical necessity when ALL of the following criteria are met: 1. Indication for use is treatment of acute angioedema attack (e.g., abdominal, facial, laryngeal) of hereditary angioedema (HAE) 2. Member is 12 years of age or older 3. Initiation requests only: e. Member has had an inadequate response (defined as an HAE attack unresponsive to treatment with generic icatibant), FDA labeled contraindication, or intolerance to treatment with ALL of the following – documentation from the medical record of the inadequate

	response, specific FDA labeled contraindication, or clinically meaningful intolerance to each product must be provided: i. Berinert ii. Icatibant (generic) iii. Kalbitor 4. Recombinant C1 Inhibitor (Ruconest) is not used concomitantly with Berinert, ecallantide (Kalbitor), icatibant (Firazyr), or sebetralstat (Ekterly) 5. Dose does not exceed 4,200 IU up to 8,400 IU in 24 hours 6. Dispensed quantity does not exceed 33,600 IU (16 vials) per 30 days[a] Duration of approval: 180 days
Sebetralstat *Ekterly*	Initiation and continuation meet the definition of medical necessity when ALL of the following criteria are met: 1. Indication for use is treatment of acute angioedema attack (e.g., abdominal, facial, laryngeal) of hereditary angioedema (HAE) 2. Member is 12 years of age or older 3. Initiation requests only: f. Member has had an inadequate response (defined as an HAE attack unresponsive to treatment with generic icatibant), FDA labeled contraindication, or intolerance to treatment with ALL of the following – documentation from the medical record of the inadequate response, specific FDA labeled contraindication, or clinically meaningful intolerance to each product must be provided: i. Berinert ii. Icatibant (generic) iii. Kalbitor a. 4. Sebetralstat (Ekterly) is not used concomitantly with Berinert, ecallantide (Kalbitor), icatibant (Firazyr), or recombinant C1 inhibitor (Ruconest) 5. Dose does not exceed 1,200 mg (4 tablets) in 24 hours 6. Dispensed quantity does not exceed 16 tablets per 30 days[a] Duration of approval: 180 days
[a] Additional quantity may be dispensed if the number of attacks and required treatment exceed supply – documentation from treatment log must be provided	

Cinryze meets the definition of medical necessity when used for the following designated Orphan Drug indication:

1. Treatment of acute antibody mediated rejection following kidney transplantation – documentation from the medical record must be provided

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Table 3: FDA-approved Dosing		
Drug	**Dosage**	**Comments**
Berotralstat (Orladeyo, Orladeyo Pellets)	Age 12 years and older: One capsule (150 mg) taken orally once daily with food. Age 2 years to less than 12 years: • 12 kg to less than 24 kg: 72 mg once daily (oral pellets) • 24 kg to less than 32 kg: 96 mg once daily (oral pellets) • 32 kg to less than 40 kg: 108 mg once daily (oral pellets) • 40 kg or greater: 132 mg once daily (oral pellets)	May reduce dose to 110 mg once daily in patients with chronic administration of P-gp or BCRP inhibitors or in patients persistant gastrointestinal reactions
Cinryze	1000 units (10 mL) IV over at least 10 minutes every 3-4 days	One unit of Cinryze corresponds to the mean quantity of C1 inhibitor present in 1 mL of normal human plasma
Haegarda	60 IU/kg SQ twice weekly	
Berinert	20 units/kg via slow IV injection at a rate of approximately 4 mL/min	Approved for both pediatric and adult patients
donidalorsen (Dawnzera)	80 mg SQ every 4 weeks	A dosage of 80 mg every 8 weeks may be considered
ecallantide (Kalbitor)	30 mg SQ administered as three 10 mg (1 mL) injections	If attack persists, an additional 30 mg dose may be administered within a 24 hour period
garadacimab (Andembry)	Initial loading dose of 400 mg (two 200 mg injections) administered subcutaneously followed by maintenance dosage of 200 mg once monthly	
icatibant (Firazyr)	30 mg SQ administered in the abdominal area	If attack persists or symptoms recur, additional 30 mg doses may be administered at intervals of at least 6 hours. Max 90 mg (3 doses)/24 hr.
lanadelumab (Takhzyro)	300 mg SQ every 2 weeks Dosing every 4 weeks may be considered in some patients	
Recombinant C1 inhibitor (Ruconest)	Body weight less than 84 kg: 50 IU/kg IV Body weight 84 kg or greater: 4200 IU (2 vials) IV Administer as a slow IV injection over 5 minutes	If the attack symptoms persist, an additional (second) dose can be administered within a 24 hr period.
sebetralstat (Ekterly)	One dose of 600 mg (2 tablets) taken orally at the earliest recognition of an HAE attack.	A second dose of 600 mg (2 tablets) may be taken 3 hours after the first dose if response is inadequate, or if symptoms worsen or recur. Maximum Recommended Dosage: 1,200 mg in any 24-hour period.
IV, intravenously; SQ, subcutaneously		

Dose Adjustment

Dosage adjustments for renal or hepatic impairment are not required.

Table 4: Drug Availability	
Drug	How Supplied

Berotralstat (Orladeyo)	Capsules: 150 mg, 110 mg Oral Pellets: 72 mg, 96 mg, 108 mg, or 132 mg in unit-dose packets
C1-INH: Cinryze, Berinert	500 unit powder for injection
C1-INH: Haegarda	2000 IU powder for injection; 3000 IU powder for injectoin
donidalorsen (Dawnzera)	80 mg/0.8 mL solution in a single-dose autoinjector
ecallantide (Kalbitor)	10 mg/mL solution for injection (10 mg vial)
garadacimab (Andembry)	200 mg/1.2 mL single-dose autoinjector and prefilled syringe
icatibant (Firazyr)	30 mg/3 mL solution for injection
lanadelumab (Takhzyro)	300 mg/2 mL (150 mg/mL) solution in a single-dose vial
Recombinant C1 inhibitor (Ruconest)	2100 IU powder for injection
sebetralstat (Ekterly)	300 mg tablet

PRECAUTIONS:

Boxed Warning-ecallantide

Anaphylaxis has been reported after administration of ecallantide. Because of the risk of anaphylaxis, ecallantide should only be administered by a health care provider with appropriate medical support to manage anaphylaxis and hereditary angioedema. Health care providers should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema, and patients should be monitored closely. Do not administer ecallantide to patients with known clinical hypersensitivity to ecallantide.

CONTRAINDICATIONS

C1-Inhibitors (Cinryze, Berinert), encallatide: Do not use in members with a history of life-threatening immediate hypersensitivity reactions, including anaphylaxis.

Hypersensitivity reactions: epinephrine should be immediately available to treat any acute severe hypersensitivity reactions following discontinuation of administration.

Thrombotic events: Thrombotic events have been reported in association with C1 inhibitor products (Cinryze and Berinert) when used off-label at high doses. Members with known risk factors for thrombotic events should be monitored closely.

Human plasma: Because C1 inhibitors (Cinryze and Berinert) are made from human blood, it may carry a risk of transmitting infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob agent). All infections thought by a health care provider possibly to have been transmitted by C1 inhibitor should be reported by the health care provider to the manufacturer. Discuss the risks and benefits of this product with the patient before prescribing or administering.

Laryngeal attacks: members should immediately seek medical attention following self-administration for the treatment of laryngeal attacks.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

J0593	Injection, lanadelumab-flyo, 1 mg
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, 1 mg
J1744	Injection, icatibant, 1 mg
J3490	Unclassified biologics (Andembry, Dawnzera only)
J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified (Ekterly and Orladeyo only)

ICD-10 Diagnosis Codes That Support Medical Necessity:

D84.1	Defects in the complement system

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

C1 esterase inhibitor (C1-INH): a protein found in the plasma part of the blood that controls C1, the first component of the complement system. It also inhibits plasmin, thrombin, and kallikrein. Deficiency of or defect in the protein causes hereditary angioedema

Hereditary Angioedema: C1 Inhibitor deficiency, an autosomal dominant disorder of the complement system manifested as recurrent episodes of edema of the skin, upper respiratory tract, and gastrointestinal tract. It may follow minor trauma, sudden changes in environmental temperature, or sudden emotional stress.

Table 5: Normal Value Ranges†		
Component	**Reference Interval**	
C1-esterase inhibitor (C1-INH) concentration	16 to 33 mg/dL	
C1-esterase functional (activity)	67% or greater: normal 41-67%: indeterminate 41% or less: abnormal	
Complement component 4 (C4)	**Age**	**Value (mg/dL)**
	0-30 days	8-30
	1 month	9-33
	2 months	9-37
	3 months	10-35
	4 months	10-49
	5 months	9-48

	6 months	12-55
	7-8 months	13-48
	9-11 months	16-51
	1 year	16-52
	2-4 years	12-47
	5-11 years	13-44
	12-17 years	14-41
	18 years and older	10-40
† Normal value ranges may vary slightly among different laboratories due to different measurements or testing different specimens. Refer to the normal value ranges of the laboratory performing the test.		

RELATED GUIDELINES:

None applicable.

OTHER:

None applicable.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 12/14/25.

GUIDELINE UPDATE INFORMATION:

07/15/09	New Medical Coverage Guideline.
01/01/10	Annual HCPCS coding update: added HCPCS code J0598.
03/15/10	Review and revision to guideline; consisting of adding new C1 Inhibitor, modifying coverage criteria and updating references.
06/15/10	Revision to guideline; consisting of adding new agent and changing the name of the guideline.
01/01/11	Revision to guideline; consisting of updating coding.
06/15/11	Review and revision to guideline; consisting of updating dosage section and references.
02/15/12	Revision to guideline; consisting of updating description, position statement, dosage and references.
01/01/13	Review and revision to guideline; consisting of revising and reformatting position statement; reformatting dosage/administration and precautions sections; adding definition including normal value reference range chart; updating references and coding.
02/15/13	Review and revision to guideline; consisting of reformatting position statement.
11/15/13	Revision to guideline consisting of adding approval durations.
02/15/14	Review and revision to guideline; consisting of updating references and reformatting position statement.
07/15/14	Revision to guideline; consisting of lowering minimum age for use of ecallantide.
11/15/14	Revision to guideline; consisting of description, position statement, dosage/administration, coding.
04/01/15	Quarterly HCPCS coding update: added code C9445 and deleted C9399.
11/01/15	Revision: ICD-9 Codes deleted.
01/01/16	Annual HCPCS coding update: added code J0596 and deleted codes C9445, J3490, and J3590.
02/15/16	Review of guideline; consisting of updating position statement, program exceptions, and references.

05/15/16	Revision of guideline; consisting of updating position statement.
10/15/16	Revision of guideline; consisting of updating position statement with FDA indication for Berinert.
02/15/17	Review and revision of guideline; consisting of updating position statement and references.
9/15/17	Revision to guideline; consisting of adding Haegarda to position statement, dose/administration, precautions/warnings, references.
10/15/17	Revision to guideline; updated description and position statement.
01/01/18	Annual HCPCS coding update: added HCPCS code C9015
2/15/18	Review to guideline; updated references.
12/15/18	Revision to guideline; consisting of adding Takhzyro (lanadelumab) to position statement, dose/administration, precautions/warnings, references.
01/01/19	Revision: HCPCS code updates. Added J0599 and C9399, and removed C9015.
02/15/19	Review to guideline; updated references.
10/01/19	Revision to position statement and updated coding
01/01/20	Revision to position statement
04/15/20	Review and revision to position statement, references
03/15/21	Review and revision to position statement, references; addition of Orladeyo to guideline
10/01/25	Review and revision to position statement, dosing/administration, precautions/warnings, coding, references; addition of Andembry and Ekterly to guideline
10/15/25	Revision to position statement
01/01/26	Revision to position statement, dosing/administration, precautions/warnings, coding, references; addition of Dawnzera to guideline
01/15/26	Revision to position statement to include preferred products (Andembry, Haegarda, generic icatibant, Orladeyo)
04/15/26	Revision to guideline; updated position statement and dosing