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Hereditary Angioedema Medical Agent Program Summary

FDA APPROVED INDICATION(S) AND DOSAGE^{1-7,17}

Agent(s)	Indication(s)	Dosage
Berinert [®] (C1 esterase inhibitor, [human]) powder for injection	Treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks in adults and pediatric patients	<ul style="list-style-type: none"> • 20 IU/kg IV administered at 4 mL/minute. Supplied as 500 IU in 10 mL • Patient may self-administer
Cinryze [®] (C1 esterase inhibitor, [human]) powder for injection	Treatment for routine prophylaxis against angioedema attacks in adult, adolescents, and pediatric patients (6 years and older) with HAE	<ul style="list-style-type: none"> • Patients 12 years and older: 1,000 Units IV administered at 1 mL/min every 3 to 4 days (Max dose 100 Units/kg every 3 to 4 days) • Patients 6 to 11 years: 500 Units IV administered at 1 mL/min every 3 to 4 days. Max dose of 1,000 Units IV every 3 to 4 days • Patient may self-administer
Firazyr [®] Sajazir [™] (icatibant) ^a injection solution	Treatment of acute attacks of HAE in adults 18 years of age and older	<ul style="list-style-type: none"> • 30 mg SC in abdominal area. Additional doses may be given at least 6 hours apart up to a maximum of 3 doses in 24 hours • Patient may self-administer
Haegarda [®] (C1 esterase inhibitor [human]) powder for injection	Routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients	<ul style="list-style-type: none"> • Administer 60 IU/kg body weight SC twice weekly (every 3 or 4 days) • Patient may self-administer
Kalbitor [®] (ecallantide) injection solution	Treatment of acute attacks of HAE in patients 12 years of age and older	<ul style="list-style-type: none"> • 30 mg (3mL) administered SC in three 10 mg (1 mL) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24-hour period • Must be administered by a health care provider
Orladeyo [™] (berotralstat) capsule	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older	<ul style="list-style-type: none"> • 150 mg orally once daily • 110 mg orally once daily for patients with moderate to severe

	Limitation of use: Safety and effectiveness for the treatment of acute HAE attacks have not been established. Orladeyo should not be used for treatment of acute attacks. Additional doses or doses higher than 150 mg once daily are not recommended due to the potential for QT prolongation.	hepatic impairment, concomitant use with P-gp or BCRP inhibitors (e.g., cyclosporine), or patients with persistent GI reactions on 150 mg daily
Ruconest [®] (C1 esterase inhibitor, [recombinant]) powder for injection	Treatment of acute attacks of HAE in adults and adolescents Limitation of Use: Effectiveness was not established in HAE patients with laryngeal attacks	<ul style="list-style-type: none"> • 50 IU/kg (maximum 4200 IU) administered via slow IV infusion over approximately five minutes. A second dose may be administered if symptoms persist (maximum 2 doses in 24 hours) • Patient may self-administer
Takhzyro [™] (lanadelumab-flyo) injection solution	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older	<ul style="list-style-type: none"> • 300 mg SC every 2 weeks. Dosing every 4 weeks may be considered if the patient is well controlled for more than 6 months • Patients may self-administer

a- generic available

CLINICAL RATIONALE

Hereditary Angioedema (HAE) is an autosomal dominant disease occurring in approximately 1 in 50,000 persons.⁹ It is characterized by recurrent episodes/attacks of nonpruritic, nonpitting, subcutaneous or submucosal edema that may involve the extremities, bowels, genitalia, trunk, face, tongue, or larynx. Attacks are self-limited, lasting two to four days, and range from inconvenient cutaneous swelling to life-threatening swelling of the larynx.¹¹ Symptoms of HAE typically begin in the first or second decade of life and persist throughout; however, any acute attack has the potential to be life-threatening.^{9,10} An acute attack that causes death is most often a result of abdominal or laryngeal involvement. Triggers for attacks vary and may be traceable to a source (e.g., minor trauma or stress); however, episodes often occur without a defined precipitating factor.⁹

Three types of HAE have been identified.^{8,9,10} Type I accounts for approximately 85% of all cases and is characterized by deficient levels of C1 esterase inhibitor (C1-INH) protein. This is in contrast to Type II (approximately 15% of all cases) where a normal level of C1-INH protein is found, but there is diminished C1-INH activity (i.e., dysfunctional C1-INH protein). Type III HAE, characterized by both normal C1-INH protein and functional levels, is rare.¹⁰

Types I and II occur as a result of a mutation in the SERPING1 gene, which codes for C1-INH, and ultimately leads to the increased generation of bradykinin. Bradykinin has been credited in all HAE types for involvement in attacks through increasing vascular permeability via the B2 receptor.⁸⁻¹⁰ Although Type III pathophysiology has not been fully elucidated, mutations in coagulation factor XII, angiotensinogen 1 (ANGPT1), and plasminogen (PLG), and effects of estrogen that affect bradykinin have been associated.¹⁵

In addition to clinical presentation and an assessment of family history, HAE diagnosis typically includes a laboratory workup of C4, C1-INH antigenic level, and C1-INH function. C4, the natural substrate for C1 esterase, is considered the single best screening test for C1-INH deficiency.^{9,10} At least 95% of patients with C1-INH deficiency will always have a reduced C4 even between attacks.¹⁶ If the patient has a normal C4, repeating the C4 during an attack increases the probability (nearly 100% of patients) that the patient's C4 will be low. In order to further distinguish between Type I and Type II HAE, the C1-INH antigenic level and/or functional activity is measured. It is recommended to repeat the blood tests to confirm diagnosis.^{9,16} The US HAE Association Medical Advisory Board (2013) also recommends that current medications that affect bradykinin and can cause angioedema (e.g., angiotensin converting-enzyme inhibitors and estrogen replacement) be evaluated and stopped when appropriate.⁸

Prior to C1-INH, icatibant, and ecallantide, treatment of acute attacks involved fresh frozen plasma and fluid/ventilation support. Currently, clinical evidence supporting the use of more than one agent used to treat acute attacks at the same time is lacking. There are multiple medications that are considered beneficial for both short- and long-term prophylaxis. There are currently two C1-INH that are approved for prophylaxis, Haegarda and Cinryze, and one kallikrein inhibitor that is approved for prophylaxis, Takhzyro. The clinical trials for Haegarda and Takhzyro included patients with a pretreatment attack rate of 3.3 and 3.5 attacks per month. The clinical trials for Cinryze required patients to have at least 2 attacks per month. The Institute for Clinical and Economic Review (ICER) completed a cost-comparison review of the three prophylaxis agents against on-demand therapy. It was found that the prophylaxis would be more cost effective for patients experiencing 3.3 attacks or more per month, while the on-demand treatment(s) would be more cost effective for patients experiencing fewer than 3.3 attacks per month.¹³

Guidelines recommend C1-INH as first-line long term prophylaxis (LTP) for pregnant or lactating HAE patients.^{8,9} Danazol and other 17 alpha-alkylated androgens have been used for long term prophylaxis with success. However, androgens have undesirable side effects (e.g., liver toxicity) and have limited use in children, pregnancy and lactation.^{8,9} Outside of the United States aminocaproic acid and tranexamic acid are approved for long-term prophylaxis of HAE.⁹

Safety¹⁻⁷

C1 esterase inhibitor products [(human-Berinert, Cinryze, Haegarda); (recombinant-Ruconest)] are contraindicated in patients who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1-INH preparations. Serious hypersensitivity reactions, including anaphylaxis may occur. Epinephrine should be immediately available for treatment of acute hypersensitivity reactions. Since Ruconest is made from the milk of transgenic rabbits, its use is contraindicated in patients with allergies to rabbits or rabbit derived products. Thrombotic events have been reported following administration of C1-INH products when used off-label at higher than labeled doses.

Anaphylaxis has been reported after administration of ecallantide (Kalbitor). The prescribing information contains a boxed warning for this, and it requires administration by a healthcare professional with appropriate medical support. Anaphylaxis occurred in 3.9% of treated patients in clinical trials.

Given the potential for airway obstruction during acute laryngeal HAE attacks, patients should be advised to seek medical attention in an appropriate healthcare facility immediately in addition to treatment with Berinert, Firazyr, or Kalbitor.

*Further safety information for each agent can be found by accessing the agent's specific prescribing information.

Guidelines

International and US HAE guidelines recommend with a high level of evidence that all patients have access to at least one of the plasma-derived/recombinant C1-INHs, icatibant, or ecallantide. They also recommend that patients should have on-demand medicine to treat two acute attacks at home and should be trained to self-administer when possible and supported by product labeling. Additionally, several guidelines note that some patients will need long term prophylaxis (LTP) in addition to on demand treatment.

The 2017 update to the international consensus from WAO and the European Association of Allergy and Clinical Immunology recommend the following:⁹

- Patients with suspected HAE should have blood levels of C1-INH function, C1-INH protein, and C4 assessed and the tests should be repeated to confirm diagnosis of HAE type 1 or 2.
- HAE attacks:
 - All attacks considered for on-demand therapy and treated with either C1-INH, ecallantide, or icatibant.
 - All patients should have sufficient on-demand medication to treat two attacks and carry medication at all times.
- HAE prophylaxis:
 - Short-term prophylaxis should be used prior to procedures that can induce an attack. C1-INH should be used as close to possible to the start of the procedure. Second line options for short term prophylaxis include androgens and fresh frozen plasma.
 - Long-term prophylaxis:
 - Should be considered for all severely symptomatic patients taking into account the disease activity, frequency of attacks, quality of life, availability of health care resources, and failure to achieve adequate control with appropriate on-demand therapy
 - All patients should be evaluated for prophylaxis at least once a year or during every office visit, and once started, efficacy and safety of long-term prophylaxis should be assessed regularly
 - Plasma-derived C1-INH is recommended as first-line therapy and androgens are second-line therapy
 - Antifibrinolytics are not recommended for long-term prophylaxis
- HAE in children and pregnancy:
 - C1-INH is recommended as first line therapy for acute attacks, short-term and long-term prophylaxis in children, pregnancy, and lactation
 - Attenuated androgens can be used second-line for short-term prophylaxis in children
 - Antifibrinolytics are preferred to androgens as second-line therapy for long-term prophylaxis in children

US HAE Association Medical Advisory Board 2013 recommends:⁸

- Patients with HAE are followed by an expert physician who is knowledgeable about the condition, experienced in managing HAE patients, and familiar with all HAE treatment options.
- Expert physicians should follow up with patients at least annually or more frequently to monitor for treatment efficacy and adverse effects.
- HAE acute attacks:

- Patients should have access to at least two doses of medicine for on-demand treatment of acute attacks.
- Early treatment options of acute attacks consist of C1-INH (Cinryze [at a dose of 1000 IU per attack] and Berinert), ecallantide, icatibant, or fresh frozen plasma. The medication selection should be individualized based on patient response and all attacks should be considered for treatment irrespective of anatomical location.
- Patients that self-administer treatment should seek medical care if the features of their attack are unusual, response to treatment is inadequate, or they experience an airway attack
- HAE prophylaxis:
 - Short-term prophylaxis:
 - C1-INH needs to be administered 1-12 hours prior to procedures or potential stressors.
 - Anabolic androgens should be administered 7-10 days before procedure or stressor.
 - On-demand treatment needs to be available regardless of use of short-term prophylaxis.
 - Long term prophylaxis:
 - Should be individualized and consider attack severity, frequency, comorbid conditions, and patient experience/preference.
 - Medication options include C1-INH as well as older alternatives of danazol, stanozolol, oxandrolone, methyl-testosterone, aminocaproic acid, or tranexamic acid.
 - HAE MAB recommends that anabolic androgens should not be used in patients that express a preference for an alternative therapy and should not be required to fail androgen therapy as a prerequisite to receiving prophylactic C1-INH therapy.
- Monitoring:
 - Attack frequency and severity should be evaluated by the physician on an ongoing basis.
 - The US HAEA MAB recommends that patients keep a record of all of their attacks, regardless of severity (mild, moderate, or severe). Regardless of format, these records should specifically identify the following 3 domains: description of attack, treatment of attack, and response to treatment.
 - The attack log should be provided to the treating physicians and reviewed on a regular basis by a means (i.e., in person or electronically) predetermined between the patient and the physician.
 - When patients self-administer or receive on-demand medications, there must be a plan to have the patient report this use in a timely manner.
 - The HAE MAB recommends that potential triggers, an updated list of current medications, to ensure that patients are not taking an angiotensin-converting enzyme inhibitor or estrogen replacement, and immunizations be reviewed when patients come into the office for visits.

Efficacy Cinryze¹⁴

One clinical trial evaluated the efficacy and safety of Cinryze in the treatment of acute attacks. The double-blind, placebo-controlled trial included 207 subjects. Eligible subjects were enrolled and asked to return to the study site within 4 hours after the onset of an acute attack. Subjects that received C1 inhibitor concentrate received 1000 units administered via IV push over a 10-min period. Eligible subjects were asked to report the severity of symptoms every 15 minutes. If symptoms were not reported as being absent or

better after 60 minutes from the initial injection, a second injection (1000 units) was administered. The primary end-point was the time from administration of the study drug to unequivocal relief of symptoms (i.e., the first of three consecutive reports of improvement). The secondary end-points included the percentage of subjects who had an onset of unequivocal relief within 4 hours after treatment, the time to complete resolution of the attack (i.e., all symptoms of swelling absent), and the effects of treatment on antigenic and functional levels of C1 inhibitor and on C4 levels. 71 eligible subjects presented with attacks and were randomly assigned to receive either Cinryze (36 subjects) or placebo (35 subjects). After study completion, 3 subjects (1 in the C1 inhibitor group and 2 in the placebo group) were judged by an independent, blinded expert to have had episodes that were not true attacks of angioedema, leaving 68 subjects remaining in the study. The estimated median time to onset of unequivocal relief was 2 hours in the Cinryze group and over 4 hours in the placebo group (estimated success rate ratio 2.41; 95% confidence interval 1.17 to 4.95; P=0.02). An open-label assessment of nanofiltered C1 inhibitor concentrate for the treatment of acute attacks showed symptom improvement within 4 hours in 93% of 447 treatments.

Takhzyro⁷

The efficacy of Takhzyro for the prevention of angioedema attacks in patients 12 years of age and older with Type I or II HAE was demonstrated in a multicenter, randomized, double-blind, placebo-controlled parallel-group study (Trial 1).

The study included 125 adult and adolescent patients with Type I or II HAE who experienced at least one investigator-confirmed attack per 4 weeks during the run-in period. Patients were randomized into 1 of 4 parallel treatment arms, stratified by baseline attack rate, in a 3:2:2:2 ratio (placebo, lanadelumab-flyo 150 mg q4wks, lanadelumab-flyo 300 mg q4wks, or lanadelumab-flyo 300 mg q2wks by subcutaneous injection) for the 26-week treatment period. Patients ≥18 years of age were required to discontinue other prophylactic HAE medications prior to entering the study; however, all patients were allowed to use rescue medications for treatment of breakthrough HAE attacks.

All Takhzyro treatment arms produced clinically meaningful and statistically significant reductions in the mean HAE attack rate compared to placebo across all primary and secondary endpoints in the Intent-to-Treat population (ITT).

Endpoint statistics	Placebo (N=41)	Takhzyro 150 mg every 4 weeks	Takhzyro 300 mg every 4 weeks	Takhzyro 300 mg every 2 weeks
Number of HAE attacks from day 0 to day 182				
Least squares mean (95% CI) monthly attack rate (attacks/4 weeks)	1.97 (1.64, 2.36)	0.48 (0.31, 0.73)	0.53 (0.36, 0.77)	0.26 (0.14, 0.46)
% reduction relative to placebo (95% CI)		76 (61, 85)	73 (59, 82)	87 (76, 93)
Adjusted p-values		<0.001	<0.001	<0.001

Number of HAE attacks requiring acute treatment from day 0 to day 182				
Least squares mean (95% CI) monthly attack rate (attacks/4 weeks)	1.64 (1.34, 2.00)	0.31 (0.18, 0.53)	0.42 (0.28, 0.65)	0.21 (0.11, 0.40)
% reduction relative to placebo (95% CI)		81 (66, 89)	74 (59, 84)	87 (75, 93)
Adjusted p-values		<0.001	<0.001	<0.001
Number of moderate or severe HAE attacks from day 0 to day 182				
Least squares mean (95% CI) monthly attack rate (attacks/4 weeks)	1.22 (0.97, 1.52)	0.36 (0.22, 0.58)	0.32 (0.20, 0.53)	0.20 (0.11, 0.39)
% reduction relative to placebo (95% CI)		70 (50, 83)	73 (54, 84)	83 (67, 92)
Adjusted p-values		<0.001	<0.001	<0.001

The mean reduction in HAE attack rate was consistently higher across the Takhzyro treatment arms compared to placebo regardless of the baseline history of prior long-term prophylaxis, laryngeal attacks, or attack rate during the run-in period.

Additional pre-defined exploratory endpoints included the percentage of patients who were attack free for the entire 26-week treatment period and the percentage of patients achieving threshold ($\geq 50\%$, $\geq 70\%$, $\geq 90\%$) reductions in HAE attack rates compared to run-in during the 26-week treatment period. A $\geq 50\%$ reduction in HAE attack rate was observed in 100% of patients on 300 mg q2wks or q4wks and 89% on 150 mg q4wks compared to 32% of placebo patients. A $\geq 70\%$ reduction in HAE attack rates was observed in 89%, 76%, and 79% of patients on 300 mg q2wks, 300 mg q4wks, and 150 mg q4wks, respectively, compared to 10% of placebo patients. A $\geq 90\%$ reduction in HAE attack rates was observed 67%, 55%, and 64% of patients on 300 mg q2wks, 300 mg q4wks, and 150 mg q4wks, respectively, compared to 5% of placebo patients.

The percentage of attack-free patients for the entire 26-week treatment period was 44%, 31%, and 39% in the Takhzyro 300 mg q2wks, 300 mg q4wks, and 150 mg q4wks groups respectively, compared to 2% of placebo patients.

Trial 2 is a rollover into an open-label extension study. Patients that completed trial 1 were eligible to be rolled over regardless of randomization in trial 1. Patients received a single dose of Takhzyro 300 mg at study entry and were followed until the first HAE attack occurred. All efficacy endpoints were exploratory in this uncontrolled, unblinded study. At week 4 post-dose, approximately 80% of patients who had been in the 300 mg every 2 weeks treatment group (N=25) in trial 1 remained attack-free. After the first HAE attack, all patients received open-label treatment with Takhzyro 300 mg every 2 weeks.

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Hereditary Angioedema Medical Drug Criteria

TARGET AGENT(S)

Berinert® (C1 Esterase Inhibitor [human])

Cinryze® (C1 Esterase Inhibitor [human])

Firazyr® (icatibant)^a

Haegarda® (C1 Esterase Inhibitor [Human])

Kalbitor® (ecallantide)

Orladeyo™ (berotralstat)

Ruconest® (C1 Esterase Inhibitor [recombinant])

Sajazir™ (icatibant)^a

Takhzyro™ (lanadelumab-flyo)

a- generic available, subject to prior authorization with quantity limit

QUANTITY LIMITS

Brand (generic)	GPI	HCPCS Code	Quantity Limit	Multisource Code
Berinert (C1 Esterase Inhibitor [Human])				
500 International Units/10 mL kit	85802022006420	J0597	5,000 International Units (10 vials)/30 days*	M, N, O, or Y
Cinryze (C1 Esterase Inhibitor [Human])				
500 Units/10 mL vial	85802022002120	J0598	10,000 Units (20 vials)/30 days	M, N, O, or Y
Firazyr, Sajazir (icatibant)^a				
30 mg/3 mL syringe	85820040102020	J1744	18 mL (6 syringes)/30 days	M, N, O, or Y
Haegarda (C1 Esterase Inhibitor [Human])				
2000 International Unit single use vial	85802022002130	J0599	See Haegarda weight-based quantity limit table below*	M, N, O, or Y
3000 International Unit single use vial	85802022002140	J0599		M, N, O, or Y
Kalbitor (ecallantide)				
10 mg/mL single use vial (box of 3 vials)	85840030002020	J1290	12 mL (4 boxes)/30 days	M, N, O, or Y
Orladeyo (berotralstat)				
110 mg capsule	85840010200120		1 capsule/day	M, N, O, or Y
150 mg capsule	85840010200130		1 capsule/day	M, N, O, or Y
Ruconest (C1 Esterase Inhibitor [recombinant])				
2100 International Unit single use vials	85802022102130	J0596	8 vials/30 days	M, N, O, or Y
Takhzyro (lanadelumab-flyo)				
300 mg/2 mL prefilled syringe	8584204020E520	J0593	4 mL (2 syringes)/28 days	M, N, O, or Y

Brand (generic)	GPI	HCPCS Code	Quantity Limit	Multisource Code
300 mg/2 mL vial	85842040202020	J0593	4 mL (2 vials)/28 days	M, N, O, or Y

*Maximum quantity limit calculation based on CDC 90 percentile for weight in adults and averaged for men and women to 238 lbs (108 kg).

a- generic available, subject to prior authorization with quantity limit

HAEGARDA WEIGHT-BASED QUANTITY LIMITS: EXTENDED DOSING TABLE

Weight (lb)	Weight (kg)	Quantity Limit of 3000 IU vials per 28 days	Quantity Limit of 2000 IU vials per 28 days	Number of 3000 IU vials used per dose	Number of 2000 IU vials used per dose
>330-365	>150-166	16	16	2	2
>293-330	>133-150	24	0	3	0
>255-293	>116-133	0	32	0	4
>220-255	>100-116	8	16	1	2
>182.6-220	>83-100	16	0	2	0
>145-182.6	>66-83	8	8	1	1
>110-145	>50-66	0	16	0	2
≥75-110	≥34-50	8	0	1	0
<75	<34	0	8	0	1

Berinert, Firazyr, icatibant, Kalbitor, Ruconest or Sajazir

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
 - A. The patient's age is within FDA labeling for the requested indication for the requested agent

OR

 - B. The prescriber has provided information in support of using the requested agent for the patient's age

AND

2. The patient has a diagnosis of Type I or Type II hereditary angioedema (HAE) evidenced by ONE of the following:
 - A. The patient's diagnosis has been confirmed with measurements of C1-INH antigenic level, C1-INH functional level, and C4 level as follows (there must be TWO separate low measurements for each test defined as below the testing laboratory's lower limit of the normal range):
 - i. Type I HAE: Two separate measurements indicating decreased quantities of C4 and decreased C1-INH antigenic level

OR

- ii. Type II HAE: Two separate measurements indicating decreased quantities of C4 and decreased C1-INH function (C1-INH antigenic level may be normal or elevated)

OR

- B. The patient’s diagnosis has been confirmed by mutation in the C1-INH gene altering protein synthesis and/or function

AND

- 3. Medications known to cause angioedema (i.e., ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate

AND

- 4. The requested agent will be used to treat acute HAE attacks

AND

- 5. If the client has preferred agent(s), then ONE of the following:

- A. The requested agent is a preferred agent

OR

- B. The patient has tried and had an inadequate response to the preferred agent(s) for on-demand use

OR

- C. The patient has an intolerance or hypersensitivity to the preferred agent(s) for on-demand use

OR

- D. The patient has an FDA labeled contraindication to the preferred agent(s) for on-demand use

AND

- 6. If the request is for one of the following brand agent(s) with an available generic equivalent (listed below), then ONE of the following:

- A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the requested brand agent

OR

- B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the requested brand agent

OR

- C. The prescriber has provided information to support the use of the requested brand agent over the generic equivalent

Brand	Generic Equivalent
Firazyr	icatibant

AND

- 7. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis

AND

- 8. The patient will NOT be using the requested agent in combination with another agent indicated for the treatment of acute HAE attacks

AND

- 9. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

- 10. ONE of the following:

- A. The requested quantity (dose) is within the program quantity limit (allows for 2 acute HAE attacks per month)

OR

- B. The requested quantity (dose) is greater than the program quantity limit and prescriber has provided information (e.g., frequency of attacks within the past 3 months has been >2 attacks per month) in support of therapy with a higher dose or quantity

Length of Approval: 6 months

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process
AND
2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
AND
3. The patient has had clinical benefit with the requested agent
AND
4. The prescriber has communicated (via any means) with the patient regarding frequency and severity of attacks and has verified that the patient does not have >1-month supply (sufficient for 2 acute HAE attacks) currently on-hand
AND
5. The patient will NOT be using the requested agent in combination with another agent indicated for the treatment of acute HAE attacks
AND
6. The patient does NOT have any FDA labeled contraindications to the requested agent
AND
7. ONE of the following:
 - a. The requested quantity (dose) is within the program quantity limit (quantity limits allow for 2 acute HAE attacks per month)
OR
 - b. The requested quantity (dose) is greater than the program quantity limit and prescriber has provided information (e.g., frequency of attacks within the past 3 months has been >2 attacks per month) in support of therapy with a higher dose or quantity

Length of Approval: 12 months

Cinryze, Haegarda, Orladeyo, or Takhzyro

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
 - A. The patient's age is within FDA labeling for the requested indication for the requested agent
OR
 - B. The prescriber has provided information in support of using the requested agent for the patient's age**AND**
2. The patient has a diagnosis of Type I or Type II hereditary angioedema (HAE) evidenced by ONE of the following:

- a. The patient's diagnosis has been confirmed with measurements of C1-INH antigenic level, C1-INH functional level, and C4 level as follows (there must be TWO separate low measurements for each test defined as below the testing laboratory's lower limit of the normal range):
 - I. Type I HAE: Two separate measurements indicating decreased quantities of C4 and decreased C1-INH antigenic level
 - OR**
 - II. Type II HAE: Two separate measurements indicating decreased quantities of C4 and decreased C1-INH function (C1-INH antigenic level may be normal or elevated)
- OR**
- B. The patient's diagnosis has been confirmed by mutation in the C1-INH gene altering protein synthesis and/or function

AND

- 3. ONE of the following:
 - a. The requested agent will be used to treat acute HAE attacks AND BOTH of the following:
 - I. The requested agent is Cinryze
 - AND**
 - II. The patient will NOT be using the requested agent in combination with another agent indicated for the treatment of acute HAE attacks
 - OR**
 - B. The requested agent will be used for prophylaxis against HAE attacks AND ALL of the following:
 - I. The patient has a history of at least three moderate to severe acute HAE attacks per month (e.g., airway swelling, severe abdominal pain, painful facial swelling)
 - AND**
 - II. The patient will NOT be using the requested agent in combination with another agent indicated for prophylaxis of HAE attacks
 - AND**
 - III. If the client has preferred agent(s), then ONE of the following:
 - a. The requested agent is a preferred agent
 - OR**
 - b. The patient has tried and had an inadequate response to the preferred agent(s) for prophylaxis use
 - OR**
 - c. The patient has an intolerance or hypersensitivity to the preferred agent(s) for prophylaxis use
 - OR**
 - d. The patient has an FDA labeled contraindication to the preferred agent(s) for prophylaxis use

AND

- 4. If Takhzyro is requested, ONE of the following:
 - A. The patient is initiating therapy with the requested agent
 - OR**
 - B. The patient has been treated with the requested agent for less than 6 consecutive months
 - OR**
 - C. The patient has been treated with the requested agent for at least 6 consecutive months **AND** ONE of the following:
 - I. The patient has been free of acute HAE attacks for at least 6 consecutive months and ONE of the following:

- I. The patient's dose will be reduced to 300 mg every 4 weeks
- OR**
- II. The prescriber has provided information in support of therapy using 300 mg every 2 weeks

OR

- II. The patient has NOT been free of acute HAE attacks for at least 6 consecutive months

AND

- 5. Medications known to cause angioedema (i.e., ACE-Inhibitors, estrogens, angiotensin receptor blockers) have been evaluated and discontinued when appropriate

AND

- 6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

- 7. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

- 8. ONE of the following:

- A. The requested quantity (dose) is within the FDA labeled or clinically supported dose AND within the quantity limit

OR

- B. The requested quantity (dose) is greater than the program quantity limit and prescriber has provided information in support of therapy with a higher dose or quantity

Length of Approval: 3 months for Cinryze, 6 months for Haegarda, 6 months for Orladeyo, and 9 months for Takhzyro

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

- 1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process

AND

- 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

- 3. ONE of the following:

- A. The requested agent was initially approved for acute HAE attacks and ALL of the following:

- i. The patient has had clinical benefit with the requested agent

AND

- ii. The prescriber has communicated (via any means) with the patient regarding frequency and severity of attacks and has verified that the patient does not have >1-month supply (sufficient for 2 acute HAE attacks) currently on-hand

AND

- iii. The patient will NOT be using the requested agent in combination with another agent indicated for the treatment of acute HAE attacks

OR

- B. The requested agent was initially approved for prophylaxis of HAE attacks and ALL of the following:

- i. ONE of the following:

1. Information has been provided that indicates the patient has had a decrease in the frequency of acute HAE attacks from baseline (prior to treatment)
 - OR**
 - 2. Information has been provided that indicates the patient has had a decrease in use of on-demand therapy
- AND**
- ii. The patient will NOT be using the requested agent in combination with another agent indicated for prophylaxis of HAE attacks
 - AND**
 - iii. If Takhzyro is requested, ONE of the following:
 1. The patient has been free of acute HAE attacks for at least 6 consecutive months and ONE of the following:
 - a. The patient's dose will be reduced to 300 mg every 4 weeks
 - OR**
 - b. The prescriber has provided information in support of therapy using 300 mg every 2 weeks
 - OR**
 2. The patient has NOT been free of acute HAE attacks for at least 6 consecutive months
- AND**
4. The patient does NOT have any FDA labeled contraindications to the requested agent
 - AND**
 - 5. ONE of the following:
 - A. The requested quantity (dose) is within the FDA labeled dose or clinically supported dose AND within the quantity limit
 - OR**
 - B. The requested quantity (dose) is greater than the program quantity limit AND prescriber has provided information in support of therapy with a higher dose or quantity

Length of Approval: 12 months

Agent(s)	Contraindication(s)
Berinerit (C1 Esterase Inhibitor [human])	Patients with history of life-threatening hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations
Cinryze (C1 Esterase Inhibitor [human])	Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis to the product.
Firazyr, Sajazir (icatibant)	None
Haegarda (C1 Esterase Inhibitor [Human])	Do not use in patients with a history of life-threatening immediate hypersensitivity reactions, including anaphylaxis to C1-INH preparations or its excipients.
Kalbitor (ecallantide)	Patients with known hypersensitivity to ecallantide
Orladeyo (berotralstat)	None

Ruconest (C1 Esterase Inhibitor [recombinant])	Patients with suspected allergy to rabbits and rabbit-derived products; patients with history of immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations.
Takhzyro (lanadelumab-flyo)	None

HAEGARDA WEIGHT-BASED QUANTITY LIMITS: EXTENDED DOSING TABLE

Weight (lb)	Weight (kg)	Quantity Limit of 3000 IU vials per 28 days	Quantity Limit of 2000 IU vials per 28 days	Number of 3000 IU vials used per dose	Number of 2000 IU vials used per dose
>330-365	>150-166	16	16	2	2
>293-330	>133-150	24	0	3	0
>255-293	>116-133	0	32	0	4
>220-255	>100-116	8	16	1	2
>182.6-220	>83-100	16	0	2	0
>145-182.6	>66-83	8	8	1	1
>110-145	>50-66	0	16	0	2
≥75-110	≥34-50	8	0	1	0
<75	<34	0	8	0	1