Hereditary Angioedema Medical Drug Criteria Program Summary

POLICY REVIEW CYCLE

Effective Date
05-01-2025

Date of Origin

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Berinert® (C1 esterase inhibitor, [human]) Freeze-dried powder for reconstitution for intravenous use	Treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks in adult and pediatric patients The safety and efficacy of Berinert for prophylactic therapy have not been established		1
CINRYZE® (C1 esterase inhibitor, [human]) Lyophilized powder for reconstitution for intravenous use	Routine prophylaxis against angioedema attacks in adults, adolescents, and pediatric patients (6 years of age and older) with Hereditary Angioedema (HAE)		2
Firazyr® Sajazir (icatibant)* Injection for subcutaneous use	Treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older	*generic available	3
HAEGARDA® (C1 esterase inhibitor [human]) Freeze-dried powder for reconstitution for	Routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in patients 6 years of age and older		4

Agent(s)	FDA Indication(s)	Notes	Ref#
subcutaneous injection			
KALBITOR ® (ecallantide) Injection for subcutaneous use	Treatment of acute attacks of hereditary angioedema (HAE) in patients 12 years of age and older		13
Orladeyo® (berotralstat) Capsule	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older Limitations of Use: The safety and effectiveness of Orladeyo for the treatment of acute HAE attacks have not been established. Orladeyo should not be used for treatment of acute HAE attacks. Additional doses or doses of Orladeyo higher than 150 mg once daily are not recommended due to the potential for QT prolongation		5
RUCONEST® (C1 esterase inhibitor, [recombinant]) Lyophilized powder for reconstitution for intravenous use	Treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE) Limitations of Use: Effectiveness was not established in HAE patients with laryngeal attacks		6
TAKHZYRO® (lanadelumab-flyo) Injection solution for subcutaneous use	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 2 years and older		7

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Hereditary Angioedema	Hereditary Angioedema (HAE) is an autosomal dominant disease. HAE 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. Angioedema attacks typically last 3 to 5 days from start to resolution, with increased morbidity and mortality if not treated with effective medication. Lack of clinical efficacy in treating HAE symptoms with antihistamines, corticosteroids, or epinephrine, is an important indicator for diagnosis.(8,9) HAE can be divided into two types, HAE due to C1INH deficiency (HAE-C1INH) and HAE with normal C1INH (HAE-nl-C1INH). HAE-C1INH can be subdivided into Type 1, characterized by deficient levels of C1 esterase inhibitor (C1-INH) protein and function, and Type 2, characterized by normal levels of C1-INH protein with diminished C1-INH activity (i.e., dysfunctional C1-INH protein). The prevalence of HAE-C1INH

	Type 1 and 2 is approximately 1 in 50,000 persons worldwide, and approximately 6,000 affected individuals in the United States.(8) HAE-C1INH Types 1 and 2 occur as a result of a mutation in the SERPING1 gene, which codes for C1-INH, and ultimately leads to the increased accumulation of bradykinin. Bradykinin has been credited in all HAE types for involvement in attacks through increasing vascular permeability via the B2 receptor.(8,9) HAE-nI-C1INH, previously referred to as Type 3 HAE, is characterized by both normal C1-INH protein and functional levels. It may also be bradykinin mediated based on the lack of response to antihistamines, corticosteroids, epinephrine, and the favorable response to bradykinin pathway-targeted medications.(8,9) HAE-nI-C1INH can be further subdivided into 5 subtypes:(8) • HAE FXII: due to mutation in F12, the gene encoding coagulation FXII • HAE-PLG: due to mutations in PLG, the gene encoding plasminogen • HAE-ANGPT1: due to mutations in ANGPT1, the gene encoding angiopoietin-1 • HAE-KNG1: due to a mutation in kininogen-1 gene • HAE-unknown: patients for whom the responsible mutation has not yet been defined The World Allergy Organization and European Academy of Allergy and Clinical Immunology (WAO/EAACI) recognize two additional subtypes of HAE-nI-C1INH. HAE-HS3ST6, which results from a mutation in the heparan sulfate 3-O-sulfotransferase 6 gene, and HAE-MYOF, which results from a mutation in the myoferlin gene.(9) Symptoms of HAE-C1INH typically begin in the first or second decade of life (sometimes as young as 2 years of age) and persist throughout the patient's lifetime. Almost all patients with HAE-C1INH will manifest symptoms by the age of 20.(8,9) 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) HAE-nI-C1INH has a similar clinical presentation to HAE-C1INH with some differences. The face and tongue are more frequently affected, with fewer abdominal symptoms. While HAE-nI-C1INH is also an autosomal dominant disorder, penetrance is variable and often lower than patients with HAE-C1INH.(8,9) 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.(8,9) In order to further distinguish between Type 1 and Type 2 HAE, the C1-INH antigenic level and/or functional activity is measured. The 2017 update to the international consensus from WAO/EAACI recommend 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. A diagnosis of Type 1 can be confirmed with a decrease in C1-INH function, C1-INH protein level, and C4 levels. A diagnosis of Type 2 can be confirmed with a decrease in C1-INH function and C4 level with an increase or normal level of C1-INH protein level.(9) The US HAE Association Medical Advisory Board (2020) indicates further repeated testing is neither necessary nor useful once C1INH deficiency has been established by laboratory testing. The guidelines also recommend evaluating current medications that affect bradykinin and that can cause angioedema (e.g., angiotensin converting-enzyme inhibitors and estrogen replacement) and stopping these when appropriate. Genetic sequencing is not usually necessary to establish the diagnosis due to the high sensitivity and specificity of biochemical tests currently available. Genetic screening may be beneficial in prenatal testing, when biochemical testing is repeatedly equivocal, or to differentiate between HAE-C1INH and acquired C1INH. The board also recommends that patients see prescribers that are HAE experts to optimize individual treatment plans, assist with coordinating care, and provide important patient and family education.(8)

	HAE-nI-C1INH does not have validated biochemical testing to confirm the diagnosis. Genetic testing may be more helpful in confirming HAE-nI-C1INH for the subtypes with common mutations. The diagnosis of HAE-nI-C1INH can be suspected in patients with normal C1INH levels and the presence of angioedema. Genetic tests for factor XII, plasminogen, angiopoetin-1, and kininogen-1 should be performed when available. A diagnosis of HAE-U should involve input from an HAE specialist.(8)
	
	On-Demand Treatment Recommendations
	
	The 2021 update to the international consensus from WAO/EAACI and the US HAE Association Medical Advisory Board 2020 indicate that all patients with laboratory confirmed HAE-C1INH should have at least two standard doses of an FDA labeled on-demand treatment for acute attacks.(8,9) Currently, clinical evidence supporting the use of more than one agent used to treat acute attacks at the same time is lacking. The 2021 update to the international consensus from WAO/EAACI recommend all HAE-C1INH attacks considered for on-demand therapy be treated with either C1-INH, ecallantide, or icatibant.(9)
	
	US HAE Association Medical Advisory Board 2020 recommends early treatment options of acute attacks for HAE-C1INH and HAE-nI-C1INH consist of plasma derived nanofiltered C1-INH (Berinert), recombinant human C1-INH (RUCONEST), ecallantide (KALBITOR), or icatibant (Firazyr). 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. Fresh frozen plasma can be used if none of the FDA labeled on-demand treatments are available. The board notes that numerous open-labeled reports have revealed successful responses for each of the on-demand treatments for HAE-n1-C1INH attacks.(8)
	
	Short-Term Prophylaxis Recommendations
	
	Patients may need prophylactic treatment prior to planned surgeries or procedures, particularly dental surgeries. Trauma and/or stress are well-known provocateurs of acute attacks.(8) The 2021 update to the international consensus from WAO/EAACI recommends that short-term prophylaxis should be used prior to procedures that can induce an attack. C1-INH should be used as close as possible to the start of the procedure. Second-line options for short-term prophylaxis include fresh frozen plasma and androgens, but neither have the safety or efficacy of intravenous C1-INH.(9)
	
	US HAE Association Medical Advisory Board 2020 recommends the following:(8)
	
	• HAE-C1INH:
	  o Short-term prophylaxis can be either a single dose of plasma derived C1INH (pdC1INH [CINRYZE, HAEGARDA]) or a course of anabolic androgen
	  o A single dose of 20 IU/kg pdC1INH can be given 1 to 12 hours before the stressor
	  o Anabolic androgens (i.e., danazol at 400 to 600 mg/day) can be administered 5-7 days before procedure or stressor and continued for 2-5 days after
	  o Recombinant human C1INH (rhC1INH [RUCONEST]) at 50 IU/kg has also been successfully used for short-term prophylaxis
	  o On-demand treatment needs to be available regardless of the use of short-term prophylaxis
	• HAE-nI-C1INH:
	  o There is no data on short-term prophylaxis
	  o For patients with a confirmed diagnosis, the same approach as HAE-C1INH may be used with the important caveat that on-demand therapy be available if needed

	Long-Term Prophylaxis Recommendations
	
	The 2021 update to the international consensus from WAO/EAACI recommends the following:(9)
	
	• 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, lanadelumab, and berotralstat are recommended as first-line therapy and androgens are second-line therapy
	• Antifibrinolytics are not recommended for long-term prophylaxis
	
	US HAE Association Medical Advisory Board 2020 recommends the following:(8)
	
	• HAE-C1INH
	  o Long-term prophylaxis should be individualized and consider attack severity, frequency, comorbid conditions, and patient experience/preference
	  o Medication options can be divided into two broad categories: first-line and second-line
	  o First-line options include C1-INH (IV CINRYZE and SC HAEGARDA), and a monoclonal inhibitor of plasma kallikrein (TAKHZYRO)
	  o Second-line options include anabolic androgens (i.e., danazol) and antifibrinolytics (epsilon aminocaproic acid or tranexamic acid)
	  o Second-line options should be reserved for when first-line agents are not available or when the patient will only accept oral therapy
	• HAE-nI-C1INH:
	  o Long-term prophylaxis has not been studied in patients with HAE-nI-C1INH
	  o There are 2 strategies frequently used for prophylaxis in patients with HAE-nI-C1INH: hormonal therapy and antifibrinolytics
	• Monitoring:
	  o Attack frequency and severity should be evaluated by the physician on an ongoing basis
	  o Patients keep a record of all of their attacks, regardless of severity (mild, moderate, or severe). These records should include description of attack, treatment of attack, response to treatment, and any adverse effects of treatment
	  o 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
	  o 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
	  o Review potential triggers, updated list of current medications, and immunizations at each office visit
	
	There are currently two plasma-derived C1-INHs that are FDA labeled for prophylaxis, HAEGARDA and CINRYZE, and one kallikrein inhibitor that is FDA labeled for prophylaxis, TAKHZYRO. Additionally, Orladeyo offers a preventative therapy to HAE patients that need an oral route of administration. 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.(11)

ICER completed a Real-World Evaluation of the prophylactic agents, noting a decrease in severe attack rates for CINRYZE, HAEGARDA, and TAKHZYRO with rates similar to those noted in clinical trials. A separate analysis of TAKHZYRO showed 64% of patients that initiated therapy with TAKHZYRO achieved an attack free status during the first 6 months of therapy. Of those that were attack free, 74% had a dose reduction to every 4 weeks.(12)

Special Population Recommendations:

The 2021 update to the international consensus from WAO/EAACI recommends the following for children and pregnant women with HAE:(9)

- C1-INH is recommended as first-line therapy for acute attacks, short-term and long-term prophylaxis in children, pregnancy, and lactation. C1-INH is considered safe and effective during pregnancy and lactation
- Attenuated androgens can be used second-line for short-term prophylaxis in children when C1-INH is unavailable. Although, US HAE Association Medical Advisory Board 2020 does NOT recommend the use of androgens for use in children.(8)
- Antifibrinolytics are preferred to androgens as second-line therapy for long-term prophylaxis in children
- Androgens and antifibrinolytics are secreted in breast milk and in contrast to androgens, tranexamic acid was found to be safe during breastfeeding

Efficacy

TAKHZYRO:(7)

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, NCT02586805).(7)

The study included 125 adult and pediatric patients (12 years of age and older) 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 every 4 weeks, lanadelumab-flyo 300 mg every 4 weeks, or lanadelumab-flyo 300 mg every 2 weeks by subcutaneous injection) for the 26-week treatment period. Patients 18 years of age and older 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.(7)

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).(7)

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.(7)

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 (greater than or equal to 50%, greater than or equal to 70%, greater than or equal to 90%) reductions in HAE attack rates compared to run-in during the 26-week treatment period. A 50% or greater reduction in HAE attack rates was observed in 100% of patients on 300 mg every 2 weeks or every 4 weeks and 89% on 150 mg every 4 weeks compared to 32% of placebo patients. A 70% or greater reduction in HAE attack rates was observed in 89%, 76%, and 79% of patients on 300 mg every 2 weeks, 300 mg every 4 weeks, and 150 mg every 4 weeks, respectively, compared to 10% of placebo patients. A 90% or greater reduction in HAE attack rates was observed 67%, 55%, and 64% of patients on 300 mg every 2 weeks, 300 mg every 4 weeks, and 150 mg every 4 weeks, respectively, compared to 5% of placebo patients.(7)

The percentage of attack-free patients for the entire 26-week treatment period was 44%, 31%, and 39% in the TAKHZYRO 300 mg every 2 weeks, 300 mg every 4 weeks, and 150 mg every 4 weeks groups respectively, compared to 2% of placebo patients.(7)

Trial 2 (NCT02741596) 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.(7)

Safety	Berinert, CINRYZE, and HAEGARDA are contraindicated in patients with a history life-threatening hypersensitivity reactions, including anaphylaxis, to C1-INH preparations or its excipients.(1,2,4) KALBITOR has a boxed warning for anaphylaxis. Due to the risk of anaphylaxis, KALBITOR should only be administered by a health care provider with appropriate medical support to manage anaphylaxis and HAE.(13)

	KALBITOR is contraindicated for use in patients with a known clinical hypersensitivity to KALBITOR.(13) RUCONEST is contraindicated in patients with the following:(6) • History of allergy to rabbits or rabbit-derived products • History of immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations Firazyr, Orladeyo, and TAKHZYRO have no FDA labeled contraindications for use.(3,5,7)

REFERENCES

Number	Reference
1	Berinert prescribing information. CSL Behring GmbH. September 2021.
2	CINRYZE prescribing information. Takeda Pharmaceuticals America, Inc. February 2023.
3	Firazyr prescribing information. Takeda Pharmaceuticals America, Inc. January 2024.
4	HAEGARDA prescribing information. CSL Behring GmbH. January 2022.
5	Orladeyo prescribing information. BioCryst Pharmaceuticals, Inc. November 2023.
6	RUCONEST prescribing information. Bioconnection B.V. April 2020.
7	TAKHZYRO prescribing information. Takeda Pharmaceuticals America, Inc. February 2023.
8	Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. The Journal of Allergy and Clinical Immunology in Practice . 2021;9(1):132-150.e3. doi:10.1016/j.jaip.2020.08.046
9	Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update. Allergy . 2022;77(7):1961-1990. doi:10.1111/all.15214
10	Reference no longer used.
11	Lin GA, Agboola F, University of Washington School of Pharmacy Modeling Group, et al. Prophylaxis for Hereditary Angioedema With Lanadelumab and C1 Inhibitors: Effectiveness and Value .; 2018. https://icer.org/wp-content/uploads/2020/10/ICER_HAE_Final_Evidence_Report_111518-1.pdf
12	Bloudek L, Jaksa A, McKenna A, et al. Observational Real-World Evidence Update; Prophylaxis of Hereditary Angioedema With Takhzyro and C1 Inhibitors: Effectiveness and Value .; 2021. https://digirepo.nlm.nih.gov/master/borndig/9918401082906676/9918401082906676.pdf
13	KALBITOR prescribing information. Takeda Pharmaceuticals America, Inc. November 2021.

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
J0597	Berinert	c1 esterase inh	500 UNIT	M ; N ; O ; Y	N		
J0598	Cinryze	c1 esterase inh	500 UNIT	M ; N ; O ; Y	N		
J1744	Firazyr ; Sajazir	icatibant acetate subcutaneous soln pref syr	30 MG/3ML	M ; N ; O ; Y	O ; Y		
J0599	Haegarda	c1 esterase inh	2000 UNIT	M ; N ; O ; Y	N		
J0599	Haegarda	c1 esterase inh	3000 UNIT	M ; N ; O ; Y	N		
J1290	Kalbitor	ecallantide inj	10 MG/ML	M ; N ; O ; Y	N		

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
	Orladeyo	berotralstat hcl cap	110 MG ; 150 MG	M ; N ; O ; Y	N		
J0596	Ruconest	c1 esterase inh	2100 UNIT	M ; N ; O ; Y	N		
J0593	Takhzyro	lanadelumab-flyo inj ; lanadelumab-flyo soln pref syringe	150 MG/ML ; 300 MG/2ML	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Berinert	c1 esterase inh	500 UNIT	10	Vials	30	DAYS	5,000 International Units (10 vials)/30 days* *Maximum quantity limit calculation based on CDC 90 percentile for weight in adults and averaged for men and women to 247.5 lbs (112.5 kg).		
Cinryze	C1 Esterase Inhibitor (Human) For IV Inj 500 Unit	500 UNIT	20	Vials	30	DAYS	1,000 IU every 3 days = 10,000 IU/30 days/500 u/vial = 20 vials		
Firazyr ; Sajazir	icatibant acetate inj 30 mg/3ml (base equivalent)	30 MG/3ML	6	Syringes	30	DAYS			
Kalbitor	ecallantide inj	10 MG/ML	4	Boxes	30	DAYS			
Orladeyo	berotralstat hcl cap	110 MG	30	Capsules	30	DAYS			
Orladeyo	berotralstat hcl cap	150 MG	30	Capsules	30	DAYS			
Ruconest	C1 Esterase Inhibitor (Recombinant) For IV Inj 2100 Unit	2100 UNIT	8	Vials	30	DAYS			
Takhzyro	lanadelumab-flyo inj	300 MG/2ML	2	Vials	28	DAYS			
Takhzyro	Lanadelumab-flyo Soln Pref Syringe	300 MG/2ML	2	Syringes	28	DAYS			
Takhzyro	lanadelumab-flyo soln pref syringe	150 MG/ML	2	Syringes	28	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Berinert	c1 esterase inh	500 UNIT	Commercial ; HIM ; ResultsRx

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Cinryze	c1 esterase inh	500 UNIT	Commercial ; HIM ; ResultsRx
Firazyr ; Sajazir	icatibant acetate subcutaneous soln pref syr	30 MG/3ML	Commercial ; HIM ; ResultsRx
Haegarda	c1 esterase inh	2000 UNIT	Commercial ; HIM ; ResultsRx
Haegarda	c1 esterase inh	3000 UNIT	Commercial ; HIM ; ResultsRx
Kalbitor	ecallantide inj	10 MG/ML	Commercial ; HIM ; ResultsRx
Orladeyo	berotralstat hcl cap	110 MG ; 150 MG	Commercial ; HIM ; ResultsRx
Ruconest	c1 esterase inh	2100 UNIT	Commercial ; HIM ; ResultsRx
Takhzyro	lanadelumab-flyo inj ; lanadelumab-flyo soln pref syringe	150 MG/ML ; 300 MG/2ML	Commercial ; HIM ; ResultsRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Berinert	c1 esterase inh	500 UNIT	Commercial ; HIM ; ResultsRx
Cinryze	C1 Esterase Inhibitor (Human) For IV Inj 500 Unit	500 UNIT	Commercial ; HIM ; ResultsRx
Firazyr ; Sajazir	icatibant acetate inj 30 mg/3ml (base equivalent)	30 MG/3ML	Commercial ; HIM ; ResultsRx
Haegarda	c1 esterase inh	3000 UNIT	Commercial ; HIM ; ResultsRx
Haegarda	C1 Esterase Inhibitor (Human) For Subcutaneous Inj 2000 Unit	2000 UNIT	Commercial ; HIM ; ResultsRx
Kalbitor	ecallantide inj	10 MG/ML	Commercial ; HIM ; ResultsRx
Orladeyo	berotralstat hcl cap	150 MG	Commercial ; HIM ; ResultsRx
Orladeyo	berotralstat hcl cap	110 MG	Commercial ; HIM ; ResultsRx
Ruconest	C1 Esterase Inhibitor (Recombinant) For IV Inj 2100 Unit	2100 UNIT	Commercial ; HIM ; ResultsRx
Takhzyro	lanadelumab-flyo inj	300 MG/2ML	Commercial ; HIM ; ResultsRx
Takhzyro	Lanadelumab-flyo Soln Pref Syringe	300 MG/2ML	Commercial ; HIM ; ResultsRx
Takhzyro	lanadelumab-flyo soln pref syringe	150 MG/ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Berinert, Firazyr, icatibant, Kalbitor, Ruconest or Sajazir	Initial Evaluation Target Agent(s) will be approved when ALL of the following are met: 1. BOTH of the following: A. ONE of the following: A. The patient has a diagnosis of hereditary angioedema (HAE) due to C1INH deficiency (HAE-C1INH [Type 1 or Type 2]) confirmed by ONE of the following: 1. The patient's diagnosis has been confirmed with measurements of C1-INH protein level, C1-INH function level, and C4 level as follows:

Module	Clinical Criteria for Approval

A. Type 1 HAE: Decreased quantities of C4 level, C1-INH protein level, and C1-INH function level OR
B. Type 2 HAE: Decreased quantities of C4 level and C1-INH function level (C1-INH protein level may be normal or elevated) OR

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

B. The patient has a diagnosis of hereditary angioedema (HAE) with normal C1INH (HAE-nI-C1INH) evidenced by BOTH of the following:

1. The patient has levels within the normal range for C1-INH protein level, C1-INH function level, and C4 level AND
2. ONE of the following:
   A. The patient's diagnosis is associated with a mutation in ONE of the following genes:
      1. Coagulation factor FXII (mutation in F12)
      2. Plasminogen
      3. Angiopoietin-1
      4. Kininogen-1
      5. Heparan sulfate 3-O-sulfotransferase 6 gene
      6. Myoferlin gene OR
   B. The patient has a diagnosis of HAE-U that has been confirmed by an HAE specialist (medical records required) AND

B. 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 ALL the preferred agent(s) for on-demand use AND

2. If the patient has an FDA labeled indication, then ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent OR
   B. There is support for using the requested agent for the patient's age for the requested indication 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 request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:

Brand	Generic Equivalent
Firazyr	icatibant

   A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
   B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
   C. There is support for the use of the requested brand agent over the generic equivalent 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 will NOT be using the requested agent in combination with another agent indicated for the treatment of acute HAE attacks (i.e., Berinert, Firazyr, icatibant, KALBITOR, RUCONEST) AND
8. The patient does NOT have any FDA labeled contraindications to the requested agent

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>Length of Approval: 6 months

NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria.

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 Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] 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. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:

<table><tr><td>Brand</td><td>Generic Equivalent</td></tr><tr><td>Firazyr</td><td>icatibant</td></tr></table>

A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
C. There is support for the use of the requested brand agent over the generic equivalent AND
5. The prescriber has communicated (via any means) with the patient regarding the frequency and severity of attacks and has verified that the patient does not have greater than 1-month supply (sufficient for 2 acute HAE attacks) currently on-hand AND
6. The patient will NOT be using the requested agent in combination with another agent indicated for the treatment of acute HAE attacks (i.e., Berinert, Firazyr, icatibant, KALBITOR, RUCONEST) AND
7. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 12 months

NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria.</td></tr>
<tr><td>Cinryze, Haegarda, Orladeyo, or Takhzyro</td><td>Initial Evaluation

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

1. ALL of the following:
A. The patient has a diagnosis of hereditary angioedema (HAE) due to C1INH deficiency [HAE-C1INH (Type 1 or Type 2)] evidenced by ONE of the following:
A. The patient's diagnosis has been confirmed with measurements of C1-INH protein level, C1-INH function level, and C4 level as follows:
1. Type 1 HAE: Decreased quantities of C4 level, C1-INH protein level, and C1-INH function level OR
2. Type 2 HAE: Decreased quantities of C4 level and C1-INH function level (C1-INH protein 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</td></tr>
</table>

Module	Clinical Criteria for Approval
	B. The requested agent is being prescribed for HAE prophylaxis AND C. 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 D. 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) OR C. The patient has an intolerance or hypersensitivity to the preferred agent(s) OR D. The patient has an FDA labeled contraindication to ALL the preferred agent(s) AND 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent OR B. There is support for using the requested agent for the patient's age for the requested indication AND 3. If TAKHZYRO is requested, ONE of the following: A. The patient is an adult or 12 years of age or older AND ONE of the following: 1. The patient is initiating therapy with the requested agent OR 2. The patient has been treated with the requested agent for less than 6 consecutive months OR 3. The patient has been treated with the requested agent for at least 6 consecutive months AND ONE of the following: A. The patient has been free of acute HAE attacks for at least 6 consecutive months and ONE of the following: 1. The patient's dose will be reduced to 300 mg every 4 weeks OR 2. There is support for 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 OR B. The patient is 6 to less than 12 years of age AND ONE of the following: 1. The patient is initiating therapy with the requested agent OR 2. The patient has been treated with the requested agent for less than 6 consecutive months OR 3. The patient has been treated with the requested agent for at least 6 consecutive months AND ONE of the following: A. The patient has been free of acute HAE attacks for at least 6 consecutive months and ONE of the following: 1. The patient's dose will be reduced to 150 mg every 4 weeks OR 2. There is support for therapy using 150 mg every 2 weeks OR 2. The patient has NOT been free of acute HAE attacks for at least 6 consecutive months OR C. The patient is 2 to less than 6 years of age AND 4. Medications known to cause angioedema (i.e., ACE-Inhibitors, estrogens, angiotensin receptor blockers) have been evaluated and discontinued when appropriate AND 5. 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 6. The patient will NOT be using the requested agent in combination with another agent indicated for prophylaxis of HAE attacks (i.e., CINRYZE, HAEGARDA, Orladeyo, TAKHZYRO) AND 7. The patient does NOT have any FDA labeled contraindications to the requested agent Length of Approval: 3 months for CINRYZE, 4 months for HAEGARDA, 6 months for Orladeyo, and 9 months for TAKHZYRO NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Clinical Criteria for Approval
	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 Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] 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 as indicated by ONE of the following: A. The patient has had a decrease in the frequency of acute HAE attacks from baseline (prior to therapy with the requested agent) OR B. The patient has had a decrease in use of on-demand therapy AND 4. The patient will NOT be using the requested agent in combination with another agent indicated for prophylaxis of HAE attacks (i.e., CINRYZE, HAEGARDA, Orladeyo, TAKHZYRO) AND 5. If TAKHZYRO is requested, ONE of the following: A. The patient is an adult or 12 years of age or older AND ONE of the following: 1. The patient is initiating therapy with the requested agent OR 2. The patient has been treated with the requested agent for less than 6 consecutive months OR 3. The patient has been treated with the requested agent for at least 6 consecutive months AND ONE of the following: A. The patient has been free of acute HAE attacks for at least 6 consecutive months and ONE of the following: 1. The patient's dose will be reduced to 300 mg every 4 weeks OR 2. There is support for therapy using 300 mg every 2 weeks OR B. The patient has NOT been free of acute HAE attacks for at least 6 consecutive months OR B. The patient is 6 to less than 12 years of age AND ONE of the following: 1. The patient is initiating therapy with the requested agent OR 2. The patient has been treated with the requested agent for less than 6 consecutive months OR 3. The patient has been treated with the requested agent for at least 6 consecutive months AND ONE of the following: A. The patient has been free of acute HAE attacks for at least 6 consecutive months and ONE of the following: 1. The patient's dose will be reduced to 150 mg every 4 weeks OR 2. There is support for therapy using 150 mg every 2 weeks OR B. The patient has NOT been free of acute HAE attacks for at least 6 consecutive months OR C. The patient is 2 to less than 6 years of age AND 6. The patient does NOT have any FDA labeled contraindications to the requested agent Length of Approval: 12 months NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Berinert, Firazyr,	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met:

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td>icatibant, Kalbitor, Ruconest or Sajazir</td><td>1. The requested quantity (dose) is within the program quantity limit (allows for 2 acute HAE attacks per month) OR
2. The requested quantity (dose) exceeds the program quantity limit and there is support for therapy with a higher dose or quantity for the requested indication (e.g., frequency of attacks within the past 3 months has been greater than 2 attacks per month)

Length of Approval: up to 12 months</td></tr>
<tr><td>Cinryze, Haegarda, Orladeyo, or Takhzyro</td><td>Quantity limit for the Target Agent(s) will be approved when ONE of the following is met:

1. The requested quantity (dose) is within the FDA labeled dosing for the requested indication AND within the quantity limit OR
2. The requested quantity (dose) exceeds the program quantity limit AND there is support for therapy with a higher dose or quantity for the requested indication

Length of Approval : up to 12 months

HAEGARDA WEIGHT-BASED QUANTITY LIMITS: EXTENDED DOSING TABLE

<table>
<tr><th>Weight

(lb)</th><th>Weight (kg)</th><th>Quantity Limit of 3000 IU vials

per 28 days</th><th>Quantity Limit of 2000 IU vials

per 28 days</th><th>Number of

3000 IU vials used per dose</th><th>Number of

2000 IU vials used per dose</th></tr>
<tr><td>greater than 330-365</td><td>greater than 150-166</td><td>16</td><td>16</td><td>2</td><td>2</td></tr>
<tr><td>greater than 293-330</td><td>greater than 133-150</td><td>24</td><td>0</td><td>3</td><td>0</td></tr>
<tr><td>greater than 255-293</td><td>greater than 116-133</td><td>0</td><td>32</td><td>0</td><td>4</td></tr>
<tr><td>greater than 220-255</td><td>greater than 100-116</td><td>8</td><td>16</td><td>1</td><td>2</td></tr>
<tr><td>greater than 182.6-220</td><td>greater than 83-100</td><td>16</td><td>0</td><td>2</td><td>0</td></tr>
<tr><td>greater than 145-182.6</td><td>greater than 66-83</td><td>8</td><td>8</td><td>1</td><td>1</td></tr>
<tr><td>greater than 110-145</td><td>greater than 50-66</td><td>0</td><td>16</td><td>0</td><td>2</td></tr>
<tr><td>greater than or equal</td><td>greater than or equal</td><td>8</td><td>0</td><td>1</td><td>0</td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval

to 75-110	to 34-50				
less than 75	less than 34	0	8	0	1