Hereditary Angioedema Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, FocusRx, KeyRx and Health Insurance Marketplace formularies.

This is a FlexRx standard and GenRx standard prior authorization.

Target agents are: Berinert, Firazyr, Haegarda, icatibant, Orladeyo, Ruconest, and Takhzyro.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
05-01-2024	10-01-2022

FDA APPROVED 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 adults and pediatric patients The safety and efficacy of Berinert for prophylactic therapy has not been established.		1
CINRYZE® (C1 esterase inhibitor, [human]) Lyophilized powder for reconstitution for intravenous use	Treatment for routine prophylaxis against angioedema attacks in adult, adolescents, and pediatric patients (6 years and older) with hereditary angioedema (HAE)		2
Firazyr® (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®	Routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in patients 6 years of age and older		4

Agent(s)	FDA Indication(s)	Notes	Ref#
(C1 esterase inhibitor [human]) Freeze-dried powder for reconstitution for subcutaneous injection			
Orladeyo® (berotralstat) Capsule	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older Limitations of use: Orladeyo should not be used for treatment of acute attacks.		5
RUCONEST® (C1 esterase inhibitor, [recombinant]) Lyophilized powder for reconstitution for intravenous use	Treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescent patients with 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 lasts 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-nI-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 I2 is approximately 1 in 50,000 persons worldwide, and approximately 6000 affected individuals in the United States. 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 generation 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 and may also be bradykinin mediated based on the lack of response to antihistamines, corticosteroids, and 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 kininogen1 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 and the European Association of Allergy and Clinical Immunology 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 isn't 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 kininogen1 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 approved 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), icatibant (Firazyr), 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. Fresh frozen plasma can be used if none of the FDA-approved on-demand treatments are available. The Board notes that numerous open-labeled reports have revealed successful responses of each of the on-demand treatment 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:
	  ○ Short-term prophylaxis can be either a single dose of plasma derived C1INH [pdC1INH (CINRYZE, HAEGARDA)] or a course of anabolic androgen
	  ○ A single dose of 20 IU/kg pdC1INH can be given 1 to 12 hours before the stressor
	  ○ 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
	  ○ Recombinant human C1INH [rhC1INH (RUCONEST)] at 50 IU/kg has also been successfully used for short-term prophylaxis
	  ○ On-demand treatment needs to be available regardless of use of short-term prophylaxis
	• HAE-nI-C1INH:
	  ○ There is no data on short-term prophylaxis
	  ○ 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
	  ○ Long-term prophylaxis should be individualized and consider attack severity, frequency, comorbid conditions, and patient experience/preference.
	  ○ Medication options can be divided into two broad categories: first-line and second-line
	  ○ First-line options include C1-INH (IV CINRYZE and SC HAEGARDA), and a monoclonal inhibitor of plasma kallikrein (TAKHZYRO)
	  ○ Second-line options include anabolic androgens (i.e., danazol) and antifibrinolytics (epsilon aminocaproic acid or tranexamic acid)
	  ○ 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:
	  ○ Long-term prophylaxis has not been studied in patients with HAE-nI-C1INH
	  ○ There are 2 strategies frequently used for prophylaxis in patients with HAE-nI-C1INH: hormonal therapy and antifibrinolytics
	• 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). These records should include description of attack, treatment of attack, response to treatment, and any adverse effects of 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
	
	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.(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 recommend 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. 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).

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.

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 (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.

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.

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.

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) RUCONEST is contraindicated in patients with the following:(6) • History of allergy to rabbits or rabbit-derived products • History of immediate hypersensistivity 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. October 2021.
4	HAEGARDA prescribing information. CSL Behring GmbH. January 2022.
5	Orladeyo prescribing information. BioCryst Pharmaceuticals, Inc. December 2020.
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, Banerji A, Bernstein JA, Castaldo AJ, Craig T, Davis-Lorton M, Frank MM, Li HH, Lumry WR, Zuraw BL. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol in Pract*. 2021 Jan;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*. July 2022; 77(7):1961-1990. doi:10.1111/all.15214
10	Fryar, Cheryl D.;Carroll, Margaret D.;Gu, Qiuping;Afful, Joseph;Ogden, Cynthia L. CDC. Anthropometric reference data for children and adults:United States, 2015-2018. Vital and health statistics. Series 3, Analytical and epidemiological studies;no. 46. January 2021. https://stacks.cdc.gov/view/cdc/100478
11	Institute for Clinical and Economic Review (ICER). Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value. Final Evidence Report. November 15, 2018.
12	Bloudek L, Jaksa A, McKenna A, Carlson J, Chen Y, Patrick A, Campbell JD. Observational Real-World Evidence Update; Prophylaxis of Hereditary Angioedema with Takhzyro and C1 Inhibitors: Effectiveness and Value. August 24, 2021. https://icer.org/assessment/hereditary-angioedema-2018/#timeline

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Orladeyo	berotralstat hcl cap	110 MG ; 150 MG	M ; N ; O ; Y	N		
Berinert	C1 Esterase Inhibitor (Human) For IV Inj Kit 500 Unit	500 UNIT	M ; N ; O ; Y	N		
Haegarda	C1 Esterase Inhibitor (Human) For Subcutaneous Inj 2000 Unit	2000 UNIT	M ; N ; O ; Y	N		
Haegarda	C1 Esterase Inhibitor (Human) For Subcutaneous Inj 3000 Unit	3000 UNIT	M ; N ; O ; Y	N		
Ruconest	C1 Esterase Inhibitor (Recombinant) For IV Inj 2100 Unit	2100 UNIT	M ; N ; O ; Y	N		
Firazyr ; Sajazir	icatibant acetate subcutaneous soln pref syr	30 MG/3ML	M ; N ; O ; Y	O ; Y		

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Takhzyro	Lanadelumab-flyo Inj 300 MG/2ML (150 MG/ML)	300 MG/2ML	M ; N ; O ; Y	N		
Takhzyro	lanadelumab-flyo soln pref syringe	150 MG/ML	M ; N ; O ; Y	N		
Takhzyro	Lanadelumab-flyo Soln Pref Syringe	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 Inhibitor (Human) For IV Inj Kit 500 Unit	500 UNIT	10	Vials	30	DAYS	based on CDC 90th percentile for men and women averaged to 247.5 lbs or 112.5 kg (112.5 kg * 20 IU/kg=2,250 IU/500 IU/bottle=4.5 or 5 bottles or 2500 units/attack x 2 attacks/month = 10 vials/28 days		
Firazyr ; Sajazir	icatibant acetate inj 30 mg/3ml (base equivalent)	30 MG/3ML	6	Syringes	30	DAYS			
Haegarda	C1 Esterase Inhibitor (Human) For Subcutaneous Inj 2000 Unit	2000 UNIT	27	Vials	28	DAYS	*QL calculation based on CDC 90 percentile for weight in adults, averaged for men and women, and rounded to the nearest even dose to reduce waste (112.5 kg individual). See Special Clinical Criteria Table ** Do not wildcard PA- detail to GPI 14	See Haegarda weight-based quantity limit table located in section titled 'Quantity Limit Clinical Criteria for Approval'.	
Haegarda	C1 Esterase Inhibitor (Human) For Subcutaneous Inj 3000 Unit	3000 UNIT	18	Vials	28	DAYS	*QL calculation based on CDC 90 percentile for weight in	See Haegarda weight-based quantity limit table	

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
							adults, averaged for men and women, and rounded to the nearest even dose to reduce waste (112.5 kg individual). See Special Clinical Criteria Table ** Do not wildcard PA- detail to GPI 14	located in section titled 'Quantity Limit Clinical Criteria for Approval'.	
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 (150 MG/ML)	300 MG/2ML	4	Vials	28	DAYS			
Takhzyro	lanadelumab-flyo soln pref syringe	150 MG/ML	2	Syringes	28	DAYS			
Takhzyro	Lanadelumab-flyo Soln Pref Syringe	300 MG/2ML	2	Syringes	28	DAYS			

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
85802022006420	Berinert	C1 Esterase Inhibitor (Human) For IV Inj Kit 500 Unit	500 UNIT	based on CDC 90th percentile for men and women averaged to 247.5 lbs or 112.5 kg (112.5 kg * 20 IU/kg=2,250 IU/500 IU/bottle=4.5 or 5 bottles or 2500 units/attack x 2 attacks/month = 10 vials/28 days			
85802022002130	Haegarda	C1 Esterase Inhibitor (Human) For Subcutaneous Inj 2000 Unit	2000 UNIT	*QL calculation based on CDC 90 percentile for weight in adults, averaged for men and women, and rounded to the nearest even dose to reduce waste (112.5 kg individual). See Special Clinical Criteria Table ** Do not wildcard PA- detail to GPI 14			
85802022002140	Haegarda	C1 Esterase Inhibitor (Human) For Subcutaneous Inj 3000 Unit	3000 UNIT	*QL calculation based on CDC 90 percentile for weight in adults, averaged for men and women, and rounded to the nearest even dose to reduce waste (112.5 kg individual). See Special Clinical Criteria Table ** Do not wildcard PA- detail to GPI 14			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Berinert	C1 Esterase Inhibitor (Human) For IV Inj Kit 500 Unit	500 UNIT	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
			Marketplace/BasicRx ; KeyRx
Firazyr ; Sajazir	icatibant acetate subcutaneous soln pref syr	30 MG/3ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Haegarda	C1 Esterase Inhibitor (Human) For Subcutaneous Inj 2000 Unit	2000 UNIT	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Haegarda	C1 Esterase Inhibitor (Human) For Subcutaneous Inj 3000 Unit	3000 UNIT	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Orladeyo	berotralstat hcl cap	110 MG ; 150 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Ruconest	C1 Esterase Inhibitor (Recombinant) For IV Inj 2100 Unit	2100 UNIT	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Takhzyro	Lanadelumab-flyo Inj 300 MG/2ML (150 MG/ML)	300 MG/2ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Takhzyro	lanadelumab-flyo soln pref syringe	150 MG/ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Takhzyro	Lanadelumab-flyo Soln Pref Syringe	300 MG/2ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Berinert	C1 Esterase Inhibitor (Human) For IV Inj Kit 500 Unit	500 UNIT	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Firazyr ; Sajazir	icatibant acetate inj 30 mg/3ml (base equivalent)	30 MG/3ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Haegarda	C1 Esterase Inhibitor (Human) For Subcutaneous Inj 2000 Unit	2000 UNIT	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Haegarda	C1 Esterase Inhibitor (Human) For Subcutaneous Inj 3000 Unit	3000 UNIT	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Orladeyo	Berotralstat HCl Cap	150 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Orladeyo	Berotralstat HCl Cap	110 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Ruconest	C1 Esterase Inhibitor (Recombinant) For IV Inj 2100 Unit	2100 UNIT	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Takhzyro	Lanadelumab-flyo Inj 300 MG/2ML (150 MG/ML)	300 MG/2ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Takhzyro	lanadelumab-flyo soln pref syringe	150 MG/ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Takhzyro	Lanadelumab-flyo Soln Pref Syringe	300 MG/2ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Berinert, Firazyr, icatibant, or Ruconest	

Preferred Agent(s)	Non-Preferred Agent(s)
icatibant	Firazyr

Initial Evaluation

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

1. The patient has a diagnosis of hereditary angioedema (HAE) evidenced by ONE of the following:
   A. For patients with HAE with C1 inhibitor deficiency/dysfunction (HAE type 1 or 2), BOTH of the following: (medical records/lab results required)
      1. C4 level below the lower limit of normal as defined by the laboratory performing the test **AND**
      2. ONE of the following:
         A. C1 inhibitor protein level below the lower limit of normal as defined by the laboratory performing the test **OR**
         B. C1 inhibitor function level below the lower limit of normal as defined by the laboratory performing the test **OR**

Module	Clinical Criteria for Approval
	B. For patients with HAE with normal C1 inhibitor (HAE-nI-C1INH, previously HAE type 3), ONE of the following: (medical records/lab results required) 1. Mutation in ONE of the following genes associated with HAE A. Coagulation factor XII; B. Plasminogen; C. Angiopoietin-1; D. Kininogen 1; E. Heparan sulfate 3-O-sulfotransferase 6; F. Myoferlin **OR** 2. Family history or personal history of angioedema AND failure to respond to chronic, high-dose antihistamine therapy **AND** 2. The requested agent will be used for treatment of acute HAE attacks **AND** 3. 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 for the requested indication **AND** 4. The requested agent will NOT be used in combination with other treatments for acute HAE attacks (e.g., Berinert, Firazyr, Sajazir, icatibant, Kalbitor, Ruconest) **AND** 5. Medications known to cause angioedema (i.e., ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate **AND** 6. ONE of the following: A. The requested agent is a preferred agent **OR** B. The patient has tried and had an inadequate response to ALL of the preferred agent(s) **OR** C. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ALL of the preferred agent(s) **OR** D. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** E. The prescriber has provided documentation that ALL of the preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** 7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist, allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 8. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If 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 **AND** 2. The requested agent is being used for treatment of acute HAE attacks **AND** 3. The patient continues to have acute HAE attacks (medical records required) **AND**

Module	Clinical Criteria for Approval
	4. The requested agent will NOT be used in combination with other treatments for acute HAE attacks (e.g., Berinert, Firazyr, Sajazir, icatibant, Kalbitor, Ruconest) **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist, allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
Haegarda, Orladeyo, Takhzyro	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of hereditary angioedema (HAE) evidenced by ONE of the following: A. For patients with HAE with C1 inhibitor deficiency/dysfunction (HAE type 1 or 2), BOTH of the following: (chart notes/lab results required) 1. C4 level below the lower limit of normal as defined by the laboratory performing the test **AND** 2. ONE of the following: A. C1 inhibitor protein level below the lower limit of normal as defined by the laboratory performing the test **OR** B. C1 inhibitor function level below the lower limit of normal as defined by the laboratory performing the test **OR** B. For patients with HAE with normal C1 inhibitor (HAE-nI-C1INH, previously HAE type 3), ONE of the following: (chart notes/lab results required) 1. Mutation in the ONE of the genes associated with HAE 1. Coagulation factor XII; 2. Plasminogen; 3. Angiopoietin-1; 4. Kininogen 1; 5. Heparan sulfate 3-O-sulfotransferase 6; 6. Myoferlin **OR** 2. Family history or personal history of angioedema AND failure to respond to chronic, high-dose antihistamine therapy **AND** 2. The requested agent will be used for prophylaxis against HAE attacks **AND** 3. 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 for the requested indication **AND** 4. The requested agent will NOT be used in combination with other agents for prophylaxis against HAE attacks (e.g., Cinryze, Haegarda, Orladeyo, Takhzyro) **AND** 5. The patient has a history of at least two severe acute HAE attacks per month (e.g., swelling of the throat, incapacitating gastrointestinal or cutaneous swelling) **AND** 6. 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: 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** 7. Medications known to cause angioedema (i.e., ACE-Inhibitors, estrogens, angiotensin receptor blockers) have been evaluated and discontinued when appropriate **AND**

Module	Clinical Criteria for Approval
	8. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist, allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 9. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval**: 12 months NOTE: If 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 **AND** 2. The requested agent is being used for prophylaxis against HAE attacks **AND** 3. Information has been provided that indicates the patient has had a decrease in the frequency of acute HAE attacks from baseline (prior to treatment) (chart notes required) **AND** 4. The requested agent will NOT be used in combination with other agents for prophylaxis against HAE attacks (e.g., Cinryze, Haegarda, Orladeyo, Takhzyro) **AND** 5. If Takhzyro is requested, 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. The prescriber has provided information in support of 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 **AND** 6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist, 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 **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Berinert, Firazyr, icatibant, or Ruconest	**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 program quantity limit (allows for 2 acute HAE attacks per month) **OR** 2. The requested quantity (dose) exceeds the program quantity limit and prescriber has provided information (e.g., frequency of attacks within the past 3 months has been greater than 2 attacks per month) in support of therapy with a higher dose or quantity **Length of Approval:** 12 months
Haegarda, Orladeyo, or Takhzyro	**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 program quantity limit (If Haegarda, prescriber must provide patient weight; refer to Haegarda weight-based quantity limit table and, if needed, extended dosing table) **OR**

Module	Clinical Criteria for Approval

2. The requested quantity (dose) exceeds the program quantity limit and prescriber has provided information in support of therapy with a higher dose or quantity

Length of Approval: 12 months

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
greater than 330-365	greater than 150-166	16	16	2	2
greater than 293-330	greater than 133-150	24	0	3	0
greater than 255-293	greater than 116-133	0	32	0	4
greater than 220-255	greater than 100-116	8	16	1	2
greater than 182.6-220	greater than 83-100	16	0	2	0
greater than 145-182.6	greater than 66-83	8	8	1	1
greater than 110-145	greater than 50-66	0	16	0	2
greater than or equal to 75-110	greater than or equal to 34-50	8	0	1	0
less than 75	less than 34	0	8	0	1