Hereditary Angioedema Prior Authorization with Quantity Limit Program Summary

This program applies to MN Medicaid.

The BCBS MN Step Therapy Supplement applies to this program for Medicaid.

FDA APPROVED INDICATION(S) AND DOSAGE[1-7]

Agent(s)	Indication(s)	Dosage
Acute or On-Demand Agents		
Berinert® (C1 esterase inhibitor, [human]) Powder for injection	Treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks in adults and pediatric patients	• 20 IU/kg IV administered at 4 mL/minute. Supplied as 500 IU in 10 mL • Patient may self-administer
Firazyr® (icatibant)[a] Injection solution	Treatment of acute attacks of HAE in adults 18 years of age and older	• 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
Ruconest® (C1 esterase inhibitor, [recombinant]) Powder for injection	Treatment of acute attacks in adults and adolescents with HAE Limitation of Use: Effectiveness was not established in HAE patients with laryngeal attacks	• 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
Prophylactic Agents		
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	• 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
Haegarda® (C1esterase inhibitor [human]) Powder for injection	Routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in patients 6 years of age and older	• Administer 60 IU/kg body weight SC twice weekly (every 3 or 4 days) • Patient may self-administer
Orladeyo® (berotralstat) Capsule	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older	• 150 mg orally once daily • 110 mg orally once daily for patients with moderate to severe hepatic impairment, concomitant use with P-gp or

	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.	BCRP inhibitors (e.g., cyclosporine), or patients with persistent GI reactions on 150 mg daily
Takhzyro® (lanadelumab-flyo) Injection solution	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older	• 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

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. Angioedema attacks typically lasts 3 to 5 days from start to resolution, with increased morbidity and mortality if not treated with effective medications. Lack of clinical efficacy in treating HAE symptoms with antihistamines, corticosteroids, or epinephrine, is an important indicator for diagnosis.[8]

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 I, characterized by deficient levels of C1 esterase inhibitor (C1-INH) protein, and type II, characterized by normal levels of C1-INH protein with diminished C1-INH activity (i.e., dysfunctional C1-INH protein). HAE-nI-C1INH, previously referred to as type III HAE, is characterized by both normal C1-INH protein and functional levels. 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

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]

HAE-C1INH 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.[8,9] HAE-nI-C1INH 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]

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 I and Type II 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.[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 2017 update to the international consensus from WAO and the European Association of Allergy and Clinical Immunology 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.[9]

The 2017 update to the international consensus from WAO and the European Association of Allergy and Clinical Immunology 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 2017 update to the international consensus from WAO and the European Association of Allergy and Clinical Immunology 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 androgens and fresh frozen plasma.[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

Long-Term Prophylaxis Recommendations
The 2017 update to the international consensus from WAO and the European Association of Allergy and Clinical Immunology 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 is 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 and SC), and a monoclonal inhibitor of plasma kallikrein (lanadelumab-flyo)
    - Second line options include anabolic androgens (i.e., danazol) and antifibrinolytics (aminocaproic acid or tranexamic acid)
    - Anabolic androgens should be reserved for when first-line agents are not available

- 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]

Special Population Recommendations:
The 2017 update to the international consensus from WAO and the European Association of Allergy and Clinical Immunology 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
- Attenuated androgens can be used second line for short-term prophylaxis in children. 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

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).

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 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 greater than or equal to 50% reduction in HAE attack rate 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 greater than or equal to 70% 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 greater than or equal to 90% 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 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 of 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[1-7]
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.

Ruconest is also contraindicated inpatients with a history of allergy to rabbits or rabbit-derived products.

Takhzyro, Orladeyo, and Firazyr (icatibant) do not carry any FDA labeled contraindications for use.

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

References

1. Berinert prescribing information. CSL Behring. March 2021.
2. Cinryze prescribing information. ViroPharma. January 2021.
3. Firazyr prescribing information. Shire. April 2020.
4. Haegarda prescribing information. CSL Behring. September 2020.
5. Orladeyo prescribing information. BioCryst Pharmaceuticals, Inc. December 2020.
6. Ruconest prescribing information. Pharming Healthcare Inc. April 2020.
7. Takhzyro prescribing information. Dyax Corp. November 2018.
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 Pract. 2021 Jan;9(1):132-150.e3. doi: 10.1016/j.jaip.2020.08.046.
9. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—The 2017 revision and update. *Allergy*. 2018;73:1575–1596. https://doi.org/10.1111/all.13384
10. CDC. Anthropometric Reference Data for Children and Adults: United States, 2011-2014. https://www.cdc.gov/nchs/data/series/sr_03/sr03_039.pdf
11. Institute for Clinical and Economic Review (ICER). Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value. Evidence Report. October 11, 2018.

Hereditary Angioedema Prior Authorization with Quantity Limit

TARGET AGENTS
Berinert® (C1 Esterase Inhibitor [Human])
Cinryze® (C1 Esterase Inhibitor [Human])
Firazyr® (icatibant)[a]
Haegarda® (C1 Esterase Inhibitor [Human])
Orladeyo™ (berotralstat)
Ruconest® (C1 Esterase Inhibitor [Recombinant])
Takhzyro™ (lanadelumab-flyo)
a- generic available, subject to prior authorization with quantity limit

Indication	PDL Preferred Agents
Treatment of acute attacks of hereditary angioedema (HAE)	Berinert
Routine prophylaxis to prevent hereditary angioedema (HAE) attacks	N/A

Brand (generic)	GPI	Quantity Limit (per day or as listed)	Multisource Code
Berinert (C1 Esterase Inhibitor [Human])			
500 International Units/10 mL kit	85802022006420	5,000 International Units (10 vials)/30 days*	M, N, O, or Y
Cinryze (C1 Esterase Inhibitor [Human])			
500 Units/10 mL vial	85802022002120	10,000 Units (20 vials)/30 days Maximum 25,000 Units (50 vials)/30 days if inadequate response to initial dosing	M, N, O, or Y
Firazyr (icatibant)[a]			
30 mg/3 mL syringe	85820040102020	18 mL (6 syringes)/30 days	M, N, O, or Y
Haegarda (C1 Esterase Inhibitor [Human])			
2000 International Unit single use vials	85802022002130	See Haegarda weight-based quantity limit table below*	M, N, O, or Y
3000 International Unit single use vials	85802022002140		M, N, O, or Y
Orladeyo (berotralstat)			
110 mg capsule	85840010200120	1 capsule	M, N, O, or Y
150 mg capsule	85840010200130	1 capsule	M, N, O, or Y
Ruconest (C1 Esterase Inhibitor [recombinant])			
2100 International Unit single use vials	85802022102130	8 vials/30 days	M, N, O, or Y
Takhzyro (lanadelumab-flyo)			
300 mg/2 mL vial	85842040202020	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).[12]
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	Quantity Limit of 2000 IU vials	Number of	Number of

		per 28 days	per 28 days	3000 IU vials used per dose	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, or Ruconest**
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 I or II), BOTH of the following: (chart notes/lab results required)
        i. C4 level below the lower limit of normal as defined by the laboratory performing the test
        AND
        ii. ONE of the following:
            a. C1 inhibitor antigenic level below the lower limit of normal as defined by the laboratory performing the test
            OR
            b. C1 inhibitor functional 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 (previously HAE type III), ONE of the following: (chart notes/lab results required)
        i. Mutation in the coagulation factor XII gene associated with HAE
        OR
        ii. 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, 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 in the Minnesota Medicaid Preferred Drug List (PDL)
    OR

B. The request is for a non-preferred agent in the Minnesota Medicaid Preferred Drug List (PDL) and ONE of the following:
    i. The patient is currently being treated with the requested agent as indicated by ALL of the following:
        a. A statement by the prescriber that the patient is currently taking the requested agent
        AND
        b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
        AND
        c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

    OR

    ii. The patient's medication history includes two preferred chemically unique agents within the same drug class in the Minnesota Medicaid Preferred Drug List (PDL) AND ONE of the following:
        a. The patient had an inadequate response to two preferred chemically unique agents within the same drug class in the Minnesota Medicaid Preferred Drug List (PDL)
        OR
        b. The prescriber has submitted an evidence-based and peer reviewed clinical practice guideline supporting the use of the requested agent over the preferred agent(s)

    OR

    iii. The patient has a documented intolerance or hypersensitivity to two preferred agents within the same drug class in the Minnesota Medicaid Preferred Drug List (PDL) that is not expected to occur with the requested agent
    OR
    iv. The patient has an FDA labeled contraindication to ALL preferred agents within the same drug class in the Minnesota Medicaid Preferred Drug List (PDL) that is not expected to occur with the requested agent
    OR
    v. The prescriber has provided documentation that the required 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
    OR
    vi. The prescriber has submitted documentation supporting the use of the non-preferred agent over the preferred agent(s)

AND

3. 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

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

AND

5. ONE of the following:
    B. The requested quantity (dose) is within the program quantity limit (allows for 2 acute HAE attacks per month)
    OR
    C. 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

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 (documentation required)
   AND
4. The requested agent will NOT be used in combination with other treatments for acute HAE attacks (e.g., Berinert, Firazyr, 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
   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

Haegarda, Orladeyo, or 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 I or II), BOTH of the following: (chart notes/lab results required)
      i. C4 level below the lower limit of normal as defined by the laboratory performing the test
         AND
      ii. ONE of the following:
         a. C1 inhibitor antigenic level below the lower limit of normal as defined by the laboratory performing the test
            OR
         b. C1 inhibitor functional 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 (previously HAE type III), ONE of the following: (chart notes/lab results required)
      i. Mutation in the coagulation factor XII gene associated with HAE

OR

ii. 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. ONE of the following:
    A. The patient patient's medication history includes danazol, aminocaproic acid, or tranexamic acid AND ONE of the following:
        i. The patient had an inadequate response to danazol, aminocaproic acid, or tranexamic acid
        OR
        ii. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over danazol, aminocaproic acid, and tranexamic acid

    OR

    B. The patient has an intolerance or hypersensitivity to danazol, aminocaproic acid, or tranexamic acid
    OR
    C. The patient has an FDA labeled contraindication to danazol, aminocaproic acid, AND tranexamic acid
    OR
    D. The patient is currently being treated with the requested agent as indicated by ALL of the following:
        i. A statement by the prescriber that the patient is currently taking the requested agent
        AND
        ii. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
        AND
        iii. The prescriber states that a change in therapy is expected to be ineffective or cause harm

    OR

    E. The prescriber has provided documentation that danazol, aminocaproic acid, and tranexamic acid 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. Medications known to cause angioedema (i.e., ACE-Inhibitors, estrogens, angiotensin receptor blockers) have been evaluated and discontinued when appropriate
AND

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
   AND
10. ONE of the following:
    A. 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
    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

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) (documentation 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. 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
   AND
7. ONE of the following:
   A. 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
   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

Cinryze
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 I or II), BOTH of the following: (chart notes/lab results required)
    i. C4 level below the lower limit of normal as defined by the laboratory performing the test
    AND
    ii. ONE of the following:
        a. C1 inhibitor antigenic level below the lower limit of normal as defined by the laboratory performing the test
        OR
        b. C1 inhibitor functional 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 (previously HAE type III), ONE of the following: (chart notes/lab results required)
    i. Mutation in the coagulation factor XII gene associated with HAE
    OR
    ii. Family history or personal history of angioedema AND failure to respond to chronic, high-dose antihistamine therapy

AND

2. ONE of the following:
    A. ALL of the following:
        i. The requested agent will be used for treatment of acute HAE attacks
        AND
        ii. The requested agent will NOT be used in combination with other treatments for acute HAE attacks (e.g., Berinert, Firazyr, icatibant, Kalbitor, Ruconest)
        AND
        iii. ONE of the following:
            1. The requested agent is a preferred agent in the Minnesota Medicaid Preferred Drug List (PDL)
            OR
            2. The request is for a non-preferred agent in the Minnesota Medicaid Preferred Drug List (PDL) and ONE of the following:
                a. The patient is currently being treated with the requested agent as indicated by ALL of the following:
                    i. A statement by the prescriber that the patient is currently taking the requested agent
                    AND
                    ii. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
                    AND
                    iii. The prescriber states that a change in therapy is expected to be ineffective or cause harm

                OR

                b. The patient's medication history includes two preferred chemically unique agents within the same drug class in the Minnesota Medicaid Preferred Drug List (PDL) AND ONE of the following:
                    i. The patient had an inadequate response to two preferred chemically unique agents within the same drug class in the Minnesota Medicaid Preferred Drug List (PDL)
                    OR

ii. The prescriber has submitted an evidence-based and peer reviewed clinical practice guideline supporting the use of the requested agent over the preferred agent(s)

OR

c. The patient has an intolerance or hypersensitivity to two preferred agents within the same drug class in the Minnesota Medicaid Preferred Drug List (PDL) that is not expected to occur with the requested agent

OR

d. The patient has an FDA labeled contraindication to ALL preferred agents within the same drug class in the Minnesota Medicaid Preferred Drug List (PDL) that is not expected to occur with the requested agent

OR

e. The prescriber has provided information that the required 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

OR

f. The prescriber has provided information supporting the use of the non-preferred agent over the preferred agent(s)

OR

B. The requested agent will be used for prophylaxis against HAE attacks AND ALL of the following:
   i. The requested agent will NOT be used in combination with other agents for prophylaxis against HAE attacks (e.g., Haegarda, Orladeyo, Takhzyro)

   AND

   ii. 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

   iii. ONE of the following:
      1. The patient patient's medication history includes danazol, aminocaproic acid, or tranexamic acid AND ONE of the following:
         a. The patient had an inadequate response to danazol, aminocaproic acid, or tranexamic acid

         OR

         b. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over danazol, aminocaproic acid, and tranexamic acid

      OR

      2. The patient has an intolerance or hypersensitivity to danazol, aminocaproic acid, or tranexamic acid

      OR

      3. The patient has an FDA labeled contraindication to danazol, aminocaproic acid, AND tranexamic acid

      OR

      4. The patient is currently being treated with the requested agent as indicated by ALL of the following:

a. A statement by the prescriber that the patient is currently taking the requested agent
AND
b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
AND
c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

OR

5. The prescriber has provided documentation that danazol, aminocaproic acid, and tranexamic acid 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

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. 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., 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
AND
7. ONE of the following:
   A. The requested quantity (dose) is within the program 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

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. ONE of the following:
   A. The requested agent was initially approved for acute HAE attacks and ALL of the following:
      i. The patient continues to have acute HAE attacks (documentation required)
      AND

ii. The requested agent will NOT be used in combination with other treatments for acute HAE attacks (e.g., Berinert, Firazyr, icatibant, Kalbitor, Ruconest)

OR

B. The requested agent was initially approved for prophylaxis of HAE attacks and ALL of the following:
   i. Information has been provided that indicates the patient has had a decrease in the frequency of acute HAE attacks from baseline (prior to treatment) (documentation required)
   AND
   ii. The requested agent will NOT be used in combination with other agents for prophylaxis against HAE attacks (e.g., Haegarda, Orladeyo, Takhzyro)

AND

3. 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
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 program 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