Hereditary Angioedema Prior Authorization with Quantity Limit Program Summary

This program applies to MN Medicaid.

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

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

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

Agent	Indication(s)	Recommended Dose
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
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
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
Haegarda® (C1esterase inhibitor [human]) powder for injection	Routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients	• Administer 60 IU/kg body weight SC twice weekly (every 3 or 4 days) • Patient may self-administer
Kalbitor® (ecallantide) injection solution	Treatment of acute attacks of HAE in patients 12 years of age and older	• 30 mg (3mL) administered SC in three 10 mg (1 mL) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24-hour period • Must be administered by a health care provider
Ruconest® (C1 esterase inhibitor, [recombinant])	Treatment of acute attacks of HAE in adults and adolescents	• 50 IU/kg (maximum 4200 IU) administered via slow IV infusion over approximately five minutes. A second dose may be

powder for injection	Limitation of Use: Effectiveness was not established in HAE patients with laryngeal attacks	administered if symptoms persist (maximum 2 doses in 24 hours) • Patient may self-administer
Takhzyro™ (lanadelumab-flyo) injection solution	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older	• 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[8-11]

Hereditary Angioedema (HAE) is an autosomal dominant disease occurring in approximately 1 in 50,000 persons. It is characterized by recurrent episodes/attacks of nonpruritic, nonpitting, subcutaneous or submucosal edema that may involve the extremities, bowels, genitalia, trunk, face, tongue, or larynx. Attacks are self-limited, lasting two to four days, and range from inconvenient cutaneous swelling to life-threatening swelling of the larynx. Symptoms of HAE typically begin in the first or second decade of life and persist throughout; however, any acute attack has the potential to be life-threatening. 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.

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

Types I and II occur as a result of one of 450 different mutations 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. Although Type III pathophysiology has not been fully elucidated, mutations in coagulation factor XII, angiopoietin 1 (ANGPT1), and plasminogen (PLG), and effects of estrogen that affect bradykinin have been associated.

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 C1INH deficiency. At least 95% of patients with C1INH deficiency will always have a reduced C4 even between attacks. If the patient has a normal C4, repeating the C4 during an attack increases the probability (nearly 100% of patients) that the patient's C4 will be low. In order to further distinguish between Type I and Type II HAE, the C1-INH antigenic level and/or functional activity is measured. It is recommended to repeat the blood tests to confirm diagnosis. The US HAE Association Medical Advisory Board (2013) also recommends that current medications that affect bradykinin and can cause angioedema (e.g., angiotensin converting-enzyme inhibitors and estrogen replacement) be evaluated and stopped when appropriate.

Prior to C1-INH, icatibant, and ecallantide, treatment of acute attacks involved fresh frozen plasma and fluid/ventilation support. Currently, clinical evidence supporting the use of more than one agent used to treat acute attacks at the same time is lacking. There are multiple medications that are considered beneficial for both short- and long-term prophylaxis. There are currently two C1-INH that are approved for prophylaxis, Haegarda and Cinryze, and one kallikrein inhibitor that is approved for prophylaxis, Takhzyro. The clinical trials for Haegarda

and Takhzyro included patients with a pretreatment attack rate of 3.3 and 3.5 attacks per month. The clinical trials for Cinryze required patients to have at least 2 attacks per month. The Institute for Clinical and Economic Review (ICER) completed a cost-comparison review of the three prophylaxis agents against on-demand therapy. It was found that the prophylaxis would be more cost effective for patients experiencing 3.3 attacks or more per month, while the on-demand treatment(s) would be more cost effective for patients experiencing fewer than 3.3 attacks per month.[13]

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

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. Serious hypersensitivity reactions, including anaphylaxis may occur. Epinephrine should be immediately available for treatment of acute hypersensitivity reactions. Since Ruconest is made from the milk of transgenic rabbits, its use is contraindicated in patients with allergies to rabbits or rabbit derived products. Thrombotic events have been reported following administration of C1-INH products when used off-label at higher than labeled doses.

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

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

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

Guidelines[8,9]
International and US HAE guidelines recommend with a high level of evidence that all patients have access to at least one of the plasma-derived/recombinant C1-INHs, icatibant, or ecallantide. They also recommend that patients should have on-demand medicine to treat two acute attacks at home and should be trained to self-administer when possible and supported by product labeling. Additionally, several guidelines note that some patients will need long term prophylaxis (LTP) in addition to on demand treatment.

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

- Patients with suspected HAE should have blood levels of C1-INH function, C1-INH protein, and C4 assessed and the tests should be repeated to confirm diagnosis of HAE type 1 or 2.
- HAE attacks:
    - All attacks considered for on-demand therapy and treated with either C1-INH, ecallantide, or icatibant.
    - All patients should have sufficient on-demand medication to treat two attacks and carry medication at all times.
- HAE prophylaxis:

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

US HAE Association Medical Advisory Board 2013 recommends:

- Patients with HAE are followed by an expert physician who is knowledgeable about the condition, experienced in managing HAE patients, and familiar with all HAE treatment options.
- Expert physicians should follow up with patients at least annually or more frequently to monitor for treatment efficacy and adverse effects.
- HAE acute attacks:
    - Patients should have access to at least two doses of medicine for on-demand treatment of acute attacks.
    - Early treatment options of acute attacks consist of C1-INH (Cinryze [at a dose of 1000 IU per attack] and Berinert), ecallantide, icatibant, or fresh frozen plasma. The medication selection should be individualized based on patient response and all attacks should be considered for treatment irrespective of anatomical location.
    - Patients that self-administer treatment should seek medical care if the features of their attack are unusual, response to treatment is inadequate, or they experience an airway attack
- HAE prophylaxis:
    - Short-term prophylaxis:
        - C1-INH needs to be administered 1-12 hours prior to procedures or potential stressors.
        - Anabolic androgens should be administered 7-10 days before procedure or stressor.
        - On-demand treatment needs to be available regardless of use of short-term prophylaxis.
    - Long term prophylaxis:
        - Should be individualized and consider attack severity, frequency, comorbid conditions, and patient experience/preference.
        - Medication options include C1-INH as well as older alternatives of danazol, stanozolol, oxandrolone, methyl-testosterone, aminocaproic acid, or tranexamic acid.

        - HAE MAB recommends that anabolic androgens should not be used in patients that express a preference for an alternative therapy and should not be required to fail androgen therapy as a prerequisite to receiving prophylactic C1-INH therapy.
- Monitoring:
    - Attack frequency and severity should be evaluated by the physician on an ongoing basis.
    - The US HAEA MAB recommends that patients keep a record of all of their attacks, regardless of severity (mild, moderate, or severe). Regardless of format, these records should specifically identify the following 3 domains: description of attack, treatment of attack, and response to treatment.
    - The attack log should be provided to the treating physicians and reviewed on a regular basis by a means (i.e., in person or electronically) predetermined between the patient and the physician.
    - When patients self-administer or receive on-demand medications, there must be a plan to have the patient report this use in a timely manner.
    - The HAE MAB recommends that potential triggers, an updated list of current medications, to ensure that patients are not taking an angiotensin-converting enzyme inhibitor or estrogen replacement, and immunizations be reviewed when patients come into the office for visits.

Efficacy
Cinryze[14]
One clinical trial evaluated the efficacy and safety of Cinryze in the treatment of acute attacks. The double-blind, placebo-controlled trial included 207 subjects. Eligible subjects were enrolled and asked to return to the study site within 4 hours after the onset of an acute attack. Subjects that received C1 inhibitor concentrate received 1000 units administered via IV push over a 10-min period. Eligible subjects were asked to report the severity of symptoms every 15 minutes. If symptoms were not reported as being absent or better after 60 minutes from the initial injection, a second injection (1000 units) was administered. The primary end-point was the time from administration of the study drug to unequivocal relief of symptoms (i.e., the first of three consecutive reports of improvement). The secondary end-points included the percentage of subjects who had an onset of unequivocal relief within 4 hours after treatment, the time to complete resolution of the attack (i.e., all symptoms of swelling absent), and the effects of treatment on antigenic and functional levels of C1 inhibitor and on C4 levels. 71 eligible subjects presented with attacks and were randomly assigned to receive either Cinryze (36 subjects) or placebo (35 subjects). After study completion, 3 subjects (1 in the C1 inhibitor group and 2 in the placebo group) were judged by an independent, blinded expert to have had episodes that were not true attacks of angioedema, leaving 68 subjects remaining in the study. The estimated median time to onset of unequivocal relief was 2 hours in the Cinryze group and over 4 hours in the placebo group (estimated success rate ratio 2.41; 95% confidence interval 1.17 to 4.95; P=0.02). An open-label assessment of nanofiltered C1 inhibitor concentrate for the treatment of acute attacks showed symptom improvement within 4 hours in 93% of 447 treatments.

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 q4wks, lanadelumab-flyo 300 mg q4wks,

or lanadelumab-flyo 300 mg q2wks by subcutaneous injection) for the 26-week treatment period. Patients ≥18 years of age were required to discontinue other prophylactic HAE medications prior to entering the study; however, all patients were allowed to use rescue medications for treatment of breakthrough HAE attacks.

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

Endpoint statistics	Placebo (N=41)	Takhzyro 150 mg every 4 weeks	Takhzyro 300 mg every 4 weeks	Takhzyro 300 mg every 2 weeks
Number of HAE attacks from day 0 to day 182				
Least squares mean (95% CI) monthly attack rate (attacks/4 weeks)	1.97 (1.64, 2.36)	0.48 (0.31, 0.73)	0.53 (0.36, 0.77)	0.26 (0.14, 0.46)
% reduction relative to placebo (95% CI)		76 (61, 85)	73 (59, 82)	87 (76, 93)
Adjusted p-values		<0.001	<0.001	<0.001
Number of HAE attacks requiring acute treatment from day 0 to day 182				
Least squares mean (95% CI) monthly attack rate (attacks/4 weeks)	1.64 (1.34, 2.00)	0.31 (0.18, 0.53)	0.42 (0.28, 0.65)	0.21 (0.11, 0.40)
% reduction relative to placebo (95% CI)		81 (66, 89)	74 (59, 84)	87 (75, 93)
Adjusted p-values		<0.001	<0.001	<0.001
Number of moderate or severe HAE attacks from day 0 to day 182				
Least squares mean (95% CI) monthly attack rate (attacks/4 weeks)	1.22 (0.97, 1.52)	0.36 (0.22, 0.58)	0.32 (0.20, 0.53)	0.20 (0.11, 0.39)
% reduction relative to placebo (95% CI)		70 (50, 83)	73 (54, 84)	83 (67, 92)
Adjusted p-values		<0.001	<0.001	<0.001

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

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

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

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

REFERENCES

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Hereditary Angioedema Prior Authorization

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

QUANTITY LIMITS

Brand (generic)	GPI	Quantity Limit	Multisource Code
Berinert (C1 Esterase Inhibitor [Human])			
500 International Units/10 mL	85802022006420	5,000 International Units (10 vials)/30 days*	M, N, O, or Y
Cinryze (C1 Esterase Inhibitor [Human])			
500 Units/10 mL	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
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 per 28 days	Quantity Limit of 2000 IU vials per 28 days	Number of 3000 IU vials used per dose	Number of 2000 IU vials used per dose
>330-365	>150-166	16	16	2	2
>293-330	>133-150	24	0	3	0
>255-293	>116-133	0	32	0	4
>220-255	>100-116	8	16	1	2
>182.6-220	>83-100	16	0	2	0
>145-182.6	>66-83	8	8	1	1
>110-145	>50-66	0	16	0	2
≥75-110	≥34-50	8	0	1	0
<75	<34	0	8	0	1

Berinert, **Firazyr, icatibant, 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. The requested agent will NOT be used in combination with other treatments for acute HAE attacks (e.g. Berinert®, Firazyr®, icatibant, Kalbitor®, Ruconest®)
    AND
4. Medications known to cause angioedema (i.e., ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate
    AND
5. 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 and is experiencing a positive therapeutic outcome AND the prescriber provides documentation that switching the member to a preferred drug is expected to cause harm to the member or that the preferred drug would be ineffective
        OR
        ii. The patient has tried and had an inadequate response to two preferred agent(s), if available, within the same drug class in the Minnesota Medicaid Preferred Drug List (PDL) as indicated by BOTH of the following:
            a. ONE of the following:
                1) Evidence of a paid claim(s) within the past 999 days
                OR
                2) The prescriber has stated that the patient has tried the preferred agent(s) in the past 999 days
            AND
            b. ONE of the following:

1) The preferred agent(s) was discontinued due to lack of effectiveness or an adverse event
OR
2) 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, FDA labeled contraindication, or hypersensitivity to the 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 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

v. The prescriber has submitted documentation supporting the use of the non-preferred agent over the preferred agent(s)

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
AND
8. ONE of the following:
    A. The requested quantity (dose) is within the program quantity limit (allows for 2 acute HAE attacks per month)
    OR
    B. The requested quantity (dose) is greater than the program quantity limit and prescriber has submitted 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 submitted 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 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. The requested agent will NOT be used in combination with other agents for prophylaxis against HAE attacks (e.g., Cinryze®, Haegarda®, Takhzyro™)
   AND
4. 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
5. ONE of the following:
   A. The patient has tried danazol, aminocaproic acid, or tranexamic acid or a drug in the same pharmacological class with the same mechanism of action AND ONE of the following:
      i. Danazol, aminocaproic acid, or tranexamic acid or a drug in the same pharmacological class with the same mechanism of action was discontinued due to lack of effectiveness or an adverse event
         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, or tranexamic acid

OR

B. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to danazol, aminocaproic acid, or tranexamic acid

OR

C. 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

D. The prescriber has provided documentation that danazol, aminocaproic acid, or 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

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

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

AND

9. 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 submitted 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®, 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 submitted 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 and is experiencing a positive therapeutic outcome AND the prescriber provides documentation that switching the member to a preferred drug is expected to cause harm to the member or that the preferred drug would be ineffective
      OR
   b. The patient has tried and had an inadequate response to two preferred agent(s), if available, within the same drug class in the Minnesota Medicaid Preferred Drug List (PDL) as indicated by BOTH of the following:
      i. ONE of the following:
         1. Evidence of a paid claim(s) within the past 999 days
            OR
         2. The prescriber has stated that the patient has tried the preferred agent(s) in the past 999 days

      AND

      ii. ONE of the following:
         1. The preferred agent(s) was discontinued due to lack of effectiveness or an adverse event
            OR
         2. 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 a documented intolerance, FDA labeled contraindication, or hypersensitivity to the 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 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
   e. The prescriber has submitted documentation 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®, 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 has tried danazol, aminocaproic acid, or tranexamic acid or a drug in the same pharmacological class with the same mechanism of action AND ONE of the following:
        a. Danazol, aminocaproic acid, or tranexamic acid or a drug in the same pharmacological class with the same mechanism of action was discontinued due to lack of effectiveness or an adverse event
        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, or tranexamic acid
    OR
    2. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to danazol, aminocaproic acid, or tranexamic acid
    OR
    3. 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
    4. The prescriber has provided documentation that danazol, aminocaproic acid, or 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. Medications known to cause angioedema (i.e., ACE-Inhibitors, estrogens, angiotensin receptor blockers) have been evaluated and discontinued when appropriate
AND
4. 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
5. The patient does NOT have any FDA labeled contraindications to the requested agent
AND
6. 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 submitted 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®, 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 submitted information in support of therapy with a higher dose or quantity

Length of Approval: 12 months

Step Therapy Supplement Program Summary

This program applies to Medicaid.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT
OBJECTIVE
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL
The requested agent will be approved when ONE of the following are met:

1. 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
2. BOTH of the following
    a. The patient's medication history includes the required prerequisite/preferred agent(s) or a drug in the same pharmacological class with the same mechanism of action as indicated by ONE of the following:
        i. Evidence of a paid claim(s) within the past 999 days
        OR
        ii. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days

    AND
    b. ONE of the following:
        i. The required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event
        OR
        ii. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over the prerequisite/preferred agent(s)

    OR
3. The prescriber has provided documentation that the required prerequisite/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

Length of Approval: As per program specific criteria