Blue Cross Blue Shield Blue Care Network of Michigan

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Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

Effective Date: 12/12/2024

Medications for Hereditary Angioedema

Drug	HCPCS
Berinert® (c1 esterase inhibitor, human)	J0597
Cinryze™ (c1 esterase inhibitor, human)	J0598
Firazyr® (icatibant acetate)	J1744
Kalbitor® (ecallantide)	J1290
Ruconest™ (c1 esterase inhibitor, recombinant)	J0596

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. Diagnosis of type 1 or type 2 hereditary angioedema (HAE) established by an immunologist, allergist, or hematologist
   b. Diagnosis confirmed by genetic testing or with all the following laboratory findings:
      i. C4 level below the limits of the laboratory's normal reference range (normal range = 16 - 58 mg/dL)
      ii. C1INH (antigenic or function) below the limits of the laboratory's normal reference range (normal range ≥ 41%)

HAE type	C4 level	C1 INH level	C1 INH function
Type 1	Low (< 30% of mean normal level)	Low (< 40% of mean normal level)	Not fully functional
Type 2	Low (< 30% of mean normal level)	Normal or elevated	Not fully functional
Type 3	Normal	Normal	Fully functional

   c. FDA approved age
   d. Products FDA approved as treatment for acute attacks will not be covered as prophylactic therapy
   e. Patients requiring acute HAE treatment beyond the quantity allowed monthly in this policy will be required to start prophylactic therapy
   f. Acute attacks (Berinert, brand name Firazyr, Kalbitor, or Ruconest only):
      i. Trial and treatment failure to generic icatibant (Firazyr)
      ii. Treatment with Ruconest will not be authorized for use in laryngeal attacks
      iii. Cannot be used in combination with other products indicated for acute HAE attacks

   OR

g. Short-term prophylaxis (i.e., patients scheduled to undergo dental work, invasive medical procedures, and surgical procedures):
OR
h. Long-term prophylaxis:
    i. A history of at least 2 HAE attacks per month OR a history of attacks that are considered severe with swelling of the face, throat, or gastrointestinal tract.
    ii. Cannot be used in combination with other products indicated for HAE prophylaxis
    iii. For Cinryze: Trial and failure, contraindication, OR intolerance to Haegarda AND Takhzyro (age appropriate)
i. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list and/or BCBSM/BCN's prior authorization and step therapy documents.

B. Quantity Limitations, Authorization Period and Renewal Criteria
a. Quantity Limits:

Drug	Quantity Limit
Berinert	20 units/kg per infusion,4 vials per dose, 30 vials per 30 days
Cinryze	1000 units q 3 to 4 days
Firazyr	Six 30 mg doses per fill; maximum of 3 doses within a 24-hour period, 6 syringes per 30 days
Kalbitor	One 30 mg dose, additional doses approved based on medical necessity, maximum of two 30 mg doses within a 24-hour period, 18 vials per 30 days
Ruconest	50 IU/kg up to a maximum dose of 4200 IU per infusion. Authorization of 2 doses will be provided. 4 doses per 30 days.

b. Initial Authorization Period: One year at a time
c. Renewal Criteria:
    i. For long-term prophylaxis: Objective data documenting at least 50% or greater in reduction of HAE attacks and/or severity (i.e., duration of attack, days of swelling)
    ii. For acute attacks: Objective data documenting at least 50% improvement in time to relief of symptoms of acute attacks and maintenance of improvement of symptoms

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia

Background Information:

- HAE is an autosomal dominant disease caused by a deficiency of the plasma protein C1 inhibitor. The incidence of HAE is estimated to be approximately 1 in 50,000 individuals. HAE due to C1 inhibitor (C1-INH) deficiency, consists of Type I HAE (C1-INH deficiency) and Type II HAE (C1-INH dysfunction). Type I is the most common, accounting for around 85%of cases. Type II occurs in approximately 15% of cases . This disease state is characterized by subcutaneous and submucosal edema involving any part of the skin and the respiratory and gastrointestinal tracts. The role of C1 inhibitor is to regulate activation of several compliment proteases, contact-system proteases, and the fibrinolytic system. During HAE attacks, these plasma proteolytic cascades are activated and several vasoactive substances such as bradykinin are generated. Bradykinin binds to receptors on endothelial cells and causes an increase in vascular permeability that results in edema.

- Angioedema attacks are often initiated by trauma, infection, and febrile illness, but many episodes occur without a known trigger. The frequency and severity of attacks varies among patients. Untreated patients have attacks every 7-14 days on average with the frequency ranging from practically never to every 3 days.

- Per the US hereditary angioedema association (HAEA) medical advisory board 2020 guidelines for the management of hereditary angioedema, diagnosis of HAE requires recognition of clinical symptoms, which include recurrent cutaneous angioedema (in the absence of urticaria), abdominal symptoms from gastrointestinal angioedema, and airway symptoms due oropharyngeal/laryngeal swelling, and if HAE is suspected based on clinical presentation appropriate testing includes measurement of serum C4 level, C1INH antigenic level, and C1INH functional level. In patients with onset of isolated angioedema symptoms after the age of 40 or with concomitant lymphoproliferative or autoimmune conditions, a C1q level is useful to help distinguish between HAE-C1INH and acquired C1INH deficiency. C1q levels are decreased in 80% of acquired C1INH deficiency and rarely low in HAE-C1INH.

- HAE with normal C1-INH antigenic levels (previously referred to as Type III HAE) is found predominantly in women. It has been suggested that HAE with normal C1-INH is caused by activating mutations in the gene for coagulation factor XII and thus not a disease of C1-esterase deficiency. Clinical trials have demonstrated that treatment with C1 inhibitors have no therapeutic effect in patients presenting with normal C1 inhibitor concentrations and function.

- Acute Treatment and Short-Term Prophylaxis

    - It is important to note that the treatment of acute attacks differs from short-term prophylaxis. Short-term prophylaxis is indicated for patients undergoing dental procedures or surgery, both of which have been known to trigger an HAE attack. Fresh-frozen plasma has been reported to have shown a benefit for this indication, but its use is controversial because of its potential to exacerbate attacks in some patients. Epinephrine may provide temporary benefits, and neither corticosteroids nor antihistamines have shown to provide meaningful benefit in acute attacks or in short-term prophylaxis. Treatment with antifibrinolytics and 17α-alkylating androgens (such as danazol and stanozolol) takes several days to take effect therefore they are not suitable for acute treatment. Berinert (C1-inhibitor replacement therapy) is approved in the US for treatment of acute HAE attacks ins adult and pediatric patients, and Kalbitor (ecallantide) is approved in the US for treatment of acute attacks in patients ≥ 12 years of age. Firazyr (icatibant) is a potent, specific and selective B2 BK receptor antagonist that has been approved by the FDA for the acute treatment of HAE in adults. Ruconest (conestat alfa) was approved in 2014 and is a C1 esterase inhibitor [recombinant] indicated for the treatment of acute attacks in adult and adolescent patients. Ruconest cannot be used to treat laryngeal attacks. Prior to these approvals, the cornerstone of therapy in the US included symptomatic relief with pain management, IV fluids and supportive care.

- Long-term Prophylaxis

    - For patients who experience more than one attack per month long-term prophylaxis is suggested. The

treatments include antifibrinolytics, 17α-alkylating androgens, fresh-frozen plasma, kallikrein inhibitors, and C1 inhibitor. Antifibrinolytics have been reported for use in prevention of HAE attacks based on low quality evidence. Rare but serious side effects have been associated with the use of these antifibrinolytic agents. The 17α-alkylating androgens were the standard of treatment and have a long term track record of efficacy; however recently updated guidelines recommend androgen use as second line therapy due to potential adverse events Cinryze is a purified, pasteurized and nanofiltered plasma-derived C1 inhibitor (human) product that has been approved by FDA for routine prophylaxis against HAE attacks and for the treatment of acute attacks in adults and adolescent patients with HAE. Haegarda is a plasma-derived C1 inhibitor (human) that was approved in June 2017 for use in the US as prophylaxis against HAE attacks in adolescent and adult patients. C1 inhibitor therapy has been used for more than 30 years in Europe to treat patients with C1 inhibitor deficiency. Takhzyro and Orladeyo are kallikrein inhibitors approved in 2018 and 2020 respectively for prophylaxis against HAE attacks.

- On August 23, 2018, the Food and Drug Administration (FDA) approved Shire's Takhzyro for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years of age or older. Takhzyro is the first human monoclonal antibody that targets plasma kallikrein to prevent attacks of edema. It differs from the current prophylactic treatments for HAE, Cinryze and Haegarda, which are both proteins designed to replace the missing C1 inhibitor in HAE patients. Orladeyo, an oral kallikrein inhibitor, was approved in December 2020 and provides the first orally administered non-steroidal option for preventing HAE attacks.

- Prior to the approval of Cinryze in 2008, danazol, an oral synthetic androgen was the only FDA approved option for prophylaxis. The international WAO/EAACI guideline for the management of hereditary angioedema (updated 2017) suggest use of androgens as second line for long-term prophylaxis. Per the US HAE Association Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema (released 9/5/2020) medications for long term prophylaxis in HAE due to a C1-INH deficiency can be divided into 2 broad categories: first-line or second-line. The first-line therapies include IV plasma derived C1-INH replacement (Cinryze), subcutaneous (SC) plasma derived C1-INH replacement (Haegarda), and a monoclonal inhibitor of plasma kallikrein (lanadelumab, Takhzyro). Second-line therapies include the anabolic androgens (ie, danazol) and antifibrinolytics (tranexamic acid or epsilon aminocaproic acid). As there are significant differences in route of administration, side effect profiles, and efficacy between these drugs, patient preference and experience need to be considered in the selection of the most appropriate therapy. Orladeyo has not been included in these guidelines except as an additional potential consideration, due to its FDA approval coming after these guidelines were published.

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Policy History		
#	Date	Change Description
2.7	Effective Date: 12/12/2024	Annual review of criteria was performed, no changes were made
2.6	Effective Date: 12/14/2023	Update to remove C1q level to align with the HAE guidelines for diagnosis of HAE
2.5	Effective Date: 12/01/2022	Update to require generic Firazyr before other acute treatment options. Changed Firazyr/Sajazir quantity limit from 12 to 6 syringes per 30 days
2.4	Effective Date: 02/10/2022	Annual review of criteria was performed, no changes were made
2.3	Effective Date: 02/04/2021	Updated to include Orladeyo. Updated specific step therapy for Cinryze. Updated preferred verbiage
2.2	Effective Date: 4/16/2020	Updated language for preferred products Added requirement to start prophylactic therapy based on maxized acute treatment
2.1	Effective Date: 05/09/2019	Updated criteria to reflect Ruconest cannot be used to treat laryngeal attacks
2.0	Effective Date: 11/01/2018	Criteria updated to include Takhzyro and add preferred product update
1.9	Effective Date: 11/09/2017	Criteria updated to include Haegarda
1.8	Effective Date: 02/09/2016	Criteria updated to include expanded Berinert indication for pediatric patients
1.7	Effective Date: 07/01/2015	UM medical management system update for BCN for Firazyr
1.6	Effective Date: 02/01/2015	UM medical management system update for BCN for Ruconest
1.5	Effective Date: 10/30/2014	Updated to reflect addition of Ruconest to the market
1.4	Effective Date: 10/01/2014	UM medical management system update for BCBSM for Berinert, Cinryze, Firazyr, Kalbitor, and Ruconest
1.3	Effective Date: 08/14/2014	Updated for expanded Kalbitor indication (now ages 12+), and indicated ages for all medications now specified in document. Expanded coverage for prescribing physicians to include allergists. Firazyr expanded to medical benefit, and HCPCS codes added for all medications.
1.2	Effective Date: 10/24/2013	Criteria update
1.1	Effective Date: 01/01/2013	UM medical management system update for BCN for Berinert
1.0	Effective Date: 05/10/2012	New Policy. UM medical management system update for BCN for Cinryze and Kalbitor

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*

Blue Cross Blue Shield/Blue Care Network of Michigan
Medication Authorization Request Form

Hereditary Angioedema - Berinert® (C1 Esterase Inhibitor) J0597, Cinryze® (C1 Esterase Inhibitor) J0598, Kalbitor® (ecallantide) J1290, Firazyr® (icatibant) J1744, Ruconest® (C1 Esterase Inhibitor) J0596, Sajazir (icatibant acetate) J1744

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This form is to be used by participating physicians to obtain coverage for Hereditary Angioedema Medications. For commercial members only, please complete this form and submit via fax to 1-877-325-5979. If you have any questions regarding this process, please contact BCBSM Provider Relations and Servicing or the Medical Drug Helpdesk at 1-800-437-3803 for assistance.

PATIENT INFORMATION	PHYSICIAN INFORMATION
Name	**Name**
ID Number	**Specialty**
D.O.B. ☐Male ☐Female **Pt weight (in kg)** **Date recorded:**_____	**Address**
Diagnosis	**City /State/Zip**
Drug Name	**Phone/Fax: P**: ( ) - **F**: ( ) -
Dose and Quantity	**NPI**
Directions	**Contact Person**
Date of Service(s)	**Contact Person Phone / Ext.**

STEP 1: **DISEASE STATE INFORMATION**

1. Is this for Initiation or Continuation of therapy? ☐ Initiation ☐ Continuation *Date patient started therapy:* _____
2. Which product is being requested?
   ☐ Brand product (Berinert, Ruconest, Kalbitor, Firazyr) ☐ Generic product (Icatibant: generic Firazyr) ☐ Sajazir
3. Who is administering this medication? ☐ Self-administration ☐ Health Care Professional
4. Site of administration? ☐ Provider office/Home infusion ☐ Other: _____
   ☐ Hospital outpatient facility (go to #4) *Reason for Hospital Outpatient administration*: _____
5. Please specify location of administration if hospital outpatient infusion: _____
6. Please provide the NPI number for the place of administration: _____

7. **Initiation AND Continuation of therapy:**
   a. Please check the patient's diagnosis: ☐ Hereditary Angioedema (HAE) ☐ Other: _____
   b. What type of Hereditary Angioedema does the patient have?
      ☐ Type 1 ☐ Type 2 ☐ Type 3 ☐ Other: _____
   c. How was the diagnosis of HAE confirmed? Note: values defined by the laboratory performing the test
      ☐ Normal C1q level, Please provide results: _____
      ☐ C4 levels below the lower limit of normal, Please provide results: _____
      ☐ C1INH antigenic level: Low, C1INH function: not fully functional, Please provide results: _____
      ☐ C1INH antigenic level: Normal/elevated, C1INH function: not fully functional, Please provide results: _____
      ☐ Other; Please list alternative test used to confirm diagnosis AND how it confirms the diagnosis: _____
   d. What is the primary indication this medication is being used to treat?
      ☐ Treatment of acute attack ☐ Long-term prophylaxis
      ☐ Short term prophylaxis ☐ Other: _____
   e. Please select which of the following applies to the patient and their need for short-term hereditary angioedema prophylaxis:
      ☐ Dental work ☐ Surgical procedures
      ☐ Invasive medical procedures ☐ Other: _____
   f. Does the patient have a history of attacks that are considered severe with swelling of the face, throat or gastrointestinal tract? ☐ Yes ☐ No
      i. If no, how many HAE attacks does the patient have per month? _____/month.
   g. ***Cinryze only for patients ≥ 12 years old:***
      Which of the following agents has the patient experienced treatment failure with for their condition?
      ☐ Haegarda ☐ Takhzyro ☐ Other, Please list name of the agent: _____
   h. **For Berinert, Ruconest, Kalbitor, Sajazir and Firazyr only:** Has the patient experienced treatment failure with GENERIC Firazyr® (icatibant) for treatment of acute attacks?
      ☐ Yes, Please specify how the patient failed icatibant therapy (for example: side effects, lack of efficacy, etc.): _____
      ☐ No
   i. ***Ruconest only***: Has the patient had laryngeal attacks from hereditary angioedema (HAE)? ☐ Yes ☐ No
   j. Will the patient be using the drug requested in combination with other products indicated for acute hereditary angioedema (HAE) attacks (for example: Kalbitor, Berinert, Firazyr, Ruconest, or icatibant)? ☐ Yes ☐ No
   k. Will the patient be on prophylactic therapy (for example: Haegarda, Takhzyro, or Cinryze, etc.) for hereditary angioedema (HAE) if they have exceeded the total monthly quantity allowed, as defined by the BCBSM medical policy for acute HAE? ☐ Yes ☐ No

8. **Continuation of therapy: (please fill out above questions as well)**
   a. Has the patient demonstrated at least a 50% improvement of acute attacks symptoms and maintenance of symptoms? ☐ yes ☐ no
   b. For long term prophylaxis, how has the patient improved?
      ☐ 50% or greater reduction in HAE attacks ☐ Reduction in duration of attack ☐ Reduction in days of swelling ☐ Other: _____

Please add any other supporting medical information necessary for our review

Coverage will not be provided if the prescribing physician's signature and date are not reflected on this document.

☐ Request for expedited review: I certify that applying the standard review time frame may seriously jeopardize the life or health of the member or the member's ability to regain maximum function

Physician's Name **Physician Signature** **Date**

Step 2: Checklist	☐ Form Completely Filled Out ☐ Attached Chart Notes	☐ Concurrent Medical Problems ☐ Prior Therapies
Step 3: Submi	**By Fax: BCBSM Specialty Pharmacy Mailbox 1-877-325-5979**	**By Mail: BCBSM Specialty Pharmacy Program P.O. Box 312320, Detroit, MI 48231-2320**

7/24/14; 12/1/14 Updated 10/15/15; 12/28/2016; 8/11/2017; 12/5/2017;10/11/2018; 11/1/2018; 6/26/2019; 3/26/2020; 10/1/2020;12/27/2021; 12/1/2022