Pharmacy Management Drug Policy

SUBJECT: Hereditary Angioedema (HAE) For Berinert, Cinryze, Firazyr, Icatibant Haegarda, Kalbitor, Ruconest, Takhzyro
POLICY NUMBER: Pharmacy-19
EFFECTIVE DATE: 8/11
LAST REVIEW DATE: 01/13/2020

If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. Medical or drug policies apply to commercial and Health Care Reform products only when a contract benefit for the specific service exists.

DESCRIPTION: Hereditary angioedema (HAE) is an autosomal dominant disease that is caused by a deficiency in functional C1 esterase inhibitor, which leads to increases in bradykinin levels. The increase in bradykinin produces an increase in vascular permeability which leads to episodes of nonpruritic, nonpitting, subcutaneous or submucosal edema. Symptoms involve the arms, legs, hands, feet, bowels, genitalia, trunk, face, tongue, or larynx and typically begin in early childhood (2-3 years of age). Attacks can be precipitated by minor trauma and stress, but may occur without an apparent trigger.

The following are measured to help confirm a diagnosis of HAE.

- Serum complement factor 4 (C4)
- C1 inhibitor (C1-INH) antigenic protein
- C1 inhibitor (C1-INH) functional level

HAE is classified into two main subtypes, Individuals with Subtype I have documented low levels of C4, C1-INH protein and C1-INH functional activity. Individuals with Subtype II have normal levels of C1-INH protein but low levels of C4 and C1-INH function. Treatment guidelines also acknowledge HAE with normal C1-INH (Subtype III) in which the C4, C1-INH protein and C1-INH functional activity are all normal.

HAE can be treated by Berinert (Human C1 Esterase Inhibitor), Cinryze (Human C1 Esterase Inhibitor), Haegarda (Human C1 Esterase Inhibitor), Kalbitor (Ecallantide), Firazyr (Icatibant), Ruconest (Recombinant C1 Esterase Inhibitor) or Takhzyro (Lanadelumab-flyo) each of which is FDA approved to reduce edema symptoms. Berinert, Cinryze, Haegarda, and Ruconest treat HAE by replacing Human C1 Esterase Inhibitor deficiencies. Kalbitor treats HAE attacks by inhibiting plasma kallkrein which cleaves high molecular weight kininogen and results in bradykinin release. Firazyr and generic Icatibant inhibits bradykinin from binding the B2 receptor. Takhzyro is a plasma kallikrein inhibitor (monoclonal antibody).

POLICY:
Based upon our assessment and review of the peer-reviewed literature Berinert, Cinryze, Firazyr, Icatibant, Haegarda, Kalbitor, Ruconest and Takhzyro have been medically proven to be effective and therefore, **medically necessary** for the prophylactic and acute attack treatment of Hereditary Angioedema (HAE) following diagnoses if specific criteria are met:

A. To be considered for drug treatment, individuals must have a confirmed diagnosis of HAE based on the following:
    1. Type 1 HAE
        a. Two separate measurements indicating decreased quantities of C4 and C1-INH and a history of angioedema **OR**

2. Type II HAE
    b. If low C4 quantity but C1-INH protein normal then determine C1-INH function and repeat C4 and C1-INH. Decreased levels of C4 and C1-INH function confirms a diagnosis of Type II HAE **OR**
3. HAE with normal C1-INH (Type III HAE)
    a. Individuals with normal levels of C4 and C1-INH both during an attack and at baseline are classified as Type III HAE. Patient must have a family history of angioedema along with documented evidence that shows:
        1. Treatment with high doses of the antihistamine cetirizine at 40 milligrams a day (or equivalent) for 1 month was not effective **OR**
        2. Demonstration of a Factor XII mutation that is associated with the disease **AND**
4. Medications known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate, regardless of HAE type **AND**
5. Medication must be prescribed by an allergist, immunologist, hematologist or dermatologist

B. Berinert specific criteria

1. Must have a diagnosis of **acute** abdominal or facial attacks associated with hereditary angioedema (progress notes required)
2. Must be used for acute attacks--Safety and efficacy as prophylactic therapy has not been established and therefore will not be covered
3. Berinert has been proven to be both safe and effective in adult and pediatric patients
4. Berinert will be reviewed under the **medical benefit** when administered by a health care professional. If the member transitions to self-administration then Berinert can be authorized under the **pharmacy benefit**.
5. Dose is 20 units per kg by IV infusion.
    a. Maximum quantity limit of 10 vials per 30 days on Rx benefit
    b. Authorization on the medical benefit will be for 1 month initially then every 6 months
    c. Authorization on the pharmacy benefit will be for 6 months at a time
    d. Recertification will require documentation of decrease in severity or duration of attacks. Documentation including frequency of administration will also be required at time of recertification to monitor for appropriate use.

C. Kalbitor specific criteria

1. Must have a diagnosis of **acute** abdominal or facial attacks associated with hereditary angioedema (progress notes required)
2. Must be used for acute attacks--Safety and efficacy as prophylactic therapy has not been established and therefore will not be covered
3. Safety and efficacy has not been established in children under the age of 12 and therefore will not be covered
4. Anaphylaxis has been reported after administration of Kalbitor. Because of the risk of anaphylaxis, it should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and HAE and is therefore covered under the **medical benefit**.

5. The recommended dose of KALBITOR is 30 mg (3 mL), administered subcutaneously in three 10 mg (1mL) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24 hour period.
6. Authorization will be for 1 month initially then every 6 months
    a. Recertification will require documentation of decrease in severity or duration of attacks. Documentation including frequency of administration will also be required at time of recertification to monitor for appropriate use

D. Cinryze specific criteria

1. Must have a diagnosis of hereditary angioedema (progress notes required)
2. Must be used as a prophylaxis – not for acute treatment
3. For long term prophylaxis, the patient must meet the following:
    a. History of at least two severe HAE attacks (i.e. airway swelling, debilitating cutaneous or gastrointestinal episodes) per month that resulted in loss of work/school productivity or ER/unscheduled doctor visits OR disability for > 5 days per month due to HAE **AND**
    b. Treatment with acute therapy (i.e. Kalbitor, Firazyr, Berinert or Ruconest) did not result in meaningful outcomes such as decreased severity of attacks, avoidance of hospitalization, etc
4. Requests for new start of Cinryze for long term prophylaxis will require documentation of therapeutic failure, severe intolerance or a contraindication to Haegarda AND Takhzyro. This step does not apply to:
    a. Requests for pediatric patient's ages 6-11 years old, as Haegarda and Takhzyro are not FDA approved for patients of those ages.
    b. Requests for short-term prophylaxis prior to medical, surgical or dental procedure.
5. Cinryze will be allowed for short-term prophylaxis if being requested prior to medical, surgical or dental procedure. Approval will be for one month only.
6. Cinryze will be reviewed under the **medical benefit** when administered by a health care professional. If the member transitions to self-administration, then Cinryze can be authorized under the **pharmacy benefit**.
7. Standard dosage for pediatric patient's ages 6-11 years old is 500 unit IV infusion over 5 minutes every 3-4 days. This dose may be adjusted according to individual response, up to 1000 unit every 3-4 days.
8. Standard dosage for adolescent and adult patients (12 years old and above) is 1000 unit IV infusion over 10 minutes every 3-4 days.
9. There is a quantity limit of 20 vials per 30 days.
    a. Requests for quantities in excess of the establish quantity limit for adolescent and adult patients (12 years old and above), will be considered based on Cinryze package labeling that states:
    For patients who have not responded adequately to 1000 unit every 3 or 4 days, doses up to 2500 unit (not exceeding 100 U/kg) every 3 or 4 days may be considered based on individual patient response.
    b. Requests will require documentation of a previous trial with the standard dosage (1000 unit) and outcome of the trial, to document the need for the increased dose.
    c. No more than 50 vials per 30 days will be authorized.

10. Authorization on either the medical benefit or the pharmacy benefit will be for 6 months.
    a. Recertification will require documentation of decrease in the severity, duration, and/or frequency of attacks. Documentation including frequency of administration will also be required at time of recertification to monitor for appropriate use
11. Safety and efficacy in children under the age of 6 has not been established and therefore will not be covered

E. Icatibant (generic for Firazyr) and Firazyr specific criteria

1. Must have a diagnosis of hereditary angioedema (progress notes required)
2. Must be used for acute episodic attacks--Safety and efficacy as prophylactic therapy has not been established and therefore will not be covered
3. Firazyr (Icatibant) has potential to attenuate antihypertensive effects of ACE inhibitors and should not be administered to patients taking ACE inhibitors since there are no clinical trials in this population
4. Standard dosing is 30mg subcutaneously injected into abdominal area; if response is inadequate or symptoms recur additional injections of 30mg may be administered at intervals of at least 6 hours with no more than 3 doses per 24 hour period
5. Quantity limit of #3 (3ml each) pre-filled syringes – 9ml/30 days.
6. Authorization will be for 6 months at a time
    a. Recertification will require documentation of decrease in severity or duration of attacks. Documentation including frequency of administration will also be required at time of recertification to monitor for appropriate use.
7. Safety and Efficacy in anyone under 18 years old is not established and therefore will not be covered.
8. Firazyr (Icatibant) can be self-administered upon recognition of an HAE attack after training under the guidance of a healthcare professional and therefore will be covered under the pharmacy benefit.
9. Requests for brand Firazyr will require documentation of therapeutic failure, severe intolerance or a contraindication to a trial with generic Icatibant.

F. Ruconest specific criteria

1. Must have a diagnosis of acute attacks associated with hereditary angioedema (progress notes required)
2. Ruconest will not be covered for laryngeal attacks as efficacy has not been established in patients with laryngeal HAE attacks
3. Safety and efficacy in children under the age of 13 has not been established and therefore will not be covered
4. Ruconest will be reviewed under the **medical benefit** when administered by a health care professional. If the member transitions to self-administration, then Ruconest can be authorized under the **pharmacy benefit**.
5. Dose is 50 IU per kg by IV injection
    a. Maximum dose is 4200 IU with no more than 2 doses within a 24 hour time period
    b. Quantity limit of 100 ml per 30 days
    c. Authorization on the medical benefit will be for 1 month initially then every 6 months
    d. Authorization on the pharmacy benefit will be for 6 months at a time

e. Recertification will require documentation of decrease in severity or duration of attacks. Documentation including frequency of administration will also be required at time of recertification to monitor for appropriate use

G. Haegarda specific criteria

1. Must have a diagnosis of hereditary angioedema (progress notes required)
2. Must be used as a prophylaxis – not for acute treatment
3. For long term prophylaxis, the patient must meet the following:
    a. History of at least two severe HAE attacks (i.e. airway swelling, debilitating cutaneous or gastrointestinal episodes) per month that resulted in loss of work/school productivity or ER/unscheduled doctor visits OR disability for > 5 days per month due to HAE **AND**
    b. Treatment with acute therapy (i.e. Kalbitor, Firazyr, Berinert or Ruconest) did not result in meaningful outcomes such as decreased severity of attacks, avoidance of hospitalization, etc
4. Haegarda will be allowed for short-term prophylaxis if being requested prior to medical, surgical or dental procedure. Approval will be for one month only.
5. Haegarda can be self-administered after training under the guidance of a healthcare professional and therefore will be covered under the **pharmacy benefit**.
6. Standard dosage is 60 International Units (IU) per kg body weight by subcutaneous injection twice weekly.
    a. Quantity limit of 16 vials per 28 days (defined as the combined total amount of 2000 unit vials AND 3000 unit vials)
    b. Requests will require documentation of patient's weight to verify requested dosing is in accordance to the FDA approved dosing.
    c. Requests for dosing every three days will require documentation of a previous trial of twice weekly dosing that did not lead to a decrease in the severity, duration and/or frequency of attacks.
7. Authorization will be for 6 months at a time.
    a. Recertification will require documentation of decrease in the severity, duration, and/or frequency of attacks. Documentation including frequency of administration will also be required at time of recertification to monitor for appropriate use.
8. Safety and efficacy in children under the age of 12 has not been established and therefore will not be covered

H. Takhzyro specific criteria

1. Must have a diagnosis of hereditary angioedema (progress notes required)
2. Must be used as a prophylaxis – not for acute treatment
3. For long term prophylaxis, the patient must meet the following:
    a. History of at least two severe HAE attacks (i.e. airway swelling, debilitating cutaneous or gastrointestinal episodes) per month that resulted in loss of work/school productivity or ER/unscheduled doctor visits OR disability for > 5 days per month due to HAE **AND**
    b. Treatment with acute therapy (i.e. Kalbitor, Firazyr, Berinert or Ruconest) did not result in meaningful outcomes such as decreased severity of attacks, avoidance of hospitalization, etc

4. Takhzyro can be self-administered after training under the guidance of a healthcare professional and therefore will be covered under the **pharmacy benefit**.
5. Standard dosage is 300mg subcutaneously every two weeks.
6. There is a quantity limit of 2ml per 28 days.
7. All recertification requests (initial and subsequent) will require documentation of the frequency and severity of attacks experienced and the frequency of administration of Takhzyro to monitor for appropriate use.
8. Initial approval will be for 9 months:
    a. If 0 attacks have occurred during the prior 6 months while on the medication, a trial with an extended dosing interval of 300mg every four weeks will be required based on package labeling which states that a dose of 300 mg every four weeks is also effective.
    b. If documentation is provided that the patient is not attack free (has experienced at least 1 attack), but has had a decrease in severity, duration, and/or frequency of attacks while on the medication compared to baseline, a dosing frequency of 300mg every 2 weeks can be continued.
    c. If documentation is provided that the patient has not experienced a decrease in severity, duration, and/or frequency of attacks while on the medication compared to baseline (no benefit from the medication), further treatment will not be authorized.
9. Subsequent recertification requests will be for 6 months at a time and will be reviewed utilizing the same criteria above:
    a. If documentation has been submitted that 0 attacks have occurred during the 6 months prior, a trial with 300mg every four weeks will be required.
    b. If documentation is provided that the patient is not attack free (has experienced at least 1 attack), but has had a decrease in severity, duration, and/or frequency of attacks while on the medication compared to baseline, a dosing frequency of 300mg every 2 weeks can be continued.
    c. If documentation is provided that the patient has not experienced a decrease in severity, duration, and/or frequency of attacks while on the medication compared to baseline (no benefit from the medication), further treatment will not be authorized.

10. Safety and efficacy in children under the age of 12 has not been established and therefore will not be covered

POLICY GUIDELINES:

1. Prior-authorization is contract dependent.
2. For contracts where Insurance Law § 4903(c-1), and Public Health Law § 4903(3-a) are applicable, if trial of preferred drug(s) is the only criterion that is not met for a given condition, and one of the following circumstances can be substantiated by the requesting provider, then trial of the preferred drug(s) will not be required.

- The required prescription drug(s) is (are) contraindicated or will likely cause an adverse reaction or physical or mental harm to the member;
- The required prescription drug is expected to be ineffective based on the known clinical history and conditions and concurrent drug regimen;
- The required prescription drug(s) was (were) previously tried while under the current or a previous health plan, or another prescription drug or drugs in the same pharmacologic class or with the same mechanism of action was (were) previously tried and such prescription drug(s) was (were) discontinued due to lack of efficacy or effectiveness, diminished effect, or an adverse event;
- The required prescription drug(s) is (are) not in the patient's best interest because it will likely cause a significant barrier to adherence to or compliance with the plan of care, will likely worsen a comorbid condition, or will likely decrease the ability to achieve or maintain reasonable functional ability in performing daily activities;
- The individual is stable on the requested prescription drug. The medical profile of the individual (age, disease state, comorbidities), along with the rational for deeming stability as it relates to standard medical practice and evidence-based practice protocols for the disease state will be taken into consideration.
- The above criteria are not applicable to requests for brand name medications that have an AB rated generic. We can require a trial of an AB-rated generic equivalent prior to providing coverage for the equivalent brand name prescription drug.

3. This policy is applicable to drugs that are included on a specific drug formulary. If a drug referenced in this policy is non-formulary, please reference the Coverage Exception Evaluation Policy for All Lines of Business Formularies policy for review guidelines.
4. A normal C4 particularly during an edema attack should make one question the diagnosis of HAE
5. Some medications may trigger or worsen angioedema events in patients with HAE and should be avoided including estrogen contraceptives, hormone replacement therapy, and ACE-Inhibitors.
6. Individuals' who are authorized for prophylactic Cinryze, Haegarda or Takhzyro and have an acute attack while on therapy, should be re-evaluated to determine if there is an identifiable cause (adherence, misdiagnosis, etc) for the breakthrough.
7. Individuals will only be authorized for **one acute** HAE medication at one time.
8. Individuals will only be authorized for **one prophylactic** HAE medication at one time.
9. The above quantity limits have been established in order to be sufficient to cover a patient in the event of an attack. Due to lack of evidence for more frequent administration, requests for quantities in excess of the established limits will not be approved. In the event that a patient is completely out of medication, a one-time override for early refill may be considered. One-time overrides will be approved after the submission of documentation (via provider progress notes, hospital progress notes, etc.) clarifying the patient's exacerbation details including date of exacerbation, date of medication administration, dose administered, as well as response.

UPDATES:

Date:	Revision:
01/2020	Revision
07/19	Revision
03/19	Revision

10/18	Revision
09/18	Revision
09/18	Revision
08/18	Revision
11/17	Revision
9/17	P&T approval
8/17	Revision
8/17	Revision
7/17	Revision
8/16	Revision
3/16	Revision
4/15	Revision
12/14	Revision
5/14	Revision
5/13	Revision
2/13	Revision
2/12	Created

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