

# DRUG DETERMINATION POLICY

**Title:** DDP-30 Hereditary Angioedema Agents

**Effective Date:** December 14, 2022



Physicians Health Plan  
PHP Insurance Company  
PHP Service Company

## Important Information - Please Read Before Using This Policy

The following policy applies to health benefit plans administered by PHP and may not be covered by all PHP plans. Please refer to the member's benefit document for specific coverage information. If there is a difference between this general information and the member's benefit document, the member's benefit document will be used to determine coverage. For example, a member's benefit document may contain a specific exclusion related to a topic addressed in a coverage policy.

Benefit determinations for individual requests require consideration of:

1. The terms of the applicable benefit document in effect on the date of service.
2. Any applicable laws and regulations.
3. Any relevant collateral source materials including coverage policies.
4. The specific facts of the particular situation.

Contact PHP Customer Service to discuss plan benefits more specifically.

### 1.0 Policy:

This policy describes the determination process for coverage of specific drugs.

This policy does not guarantee or approve benefits. Coverage depends on the specific benefit plan. Drug Determination Policies are not recommendations for treatment and should not be used as treatment guidelines.

### 2.0 Background or Purpose:

Hereditary Angioedema Agents are specialty drugs indicated for acute angioedema attacks and prevention of attacks are associated with some adverse effects. These criteria were developed and implemented to ensure appropriate use for the intended diagnoses and severity of symptoms.

### 3.0 Clinical Determination Guidelines:

Document the following with chart notes:

- I. Hereditary Angioedema [must meet all listed below]:
  - A. Age:
    1. Ruconest intravenous (C1 esterase Inhibitor, recombinant IV): at least 13 years.
    2. Firazyr subcutaneous (icatibant SQ): at least two years.
    3. Berinert intravenous (C1 Esterase Inhibitor Human IV): at least five years.
    4. Cinryz intravenous (C1 Inhibitor Human IV): at least two years.
    5. Kalbitor subcutaneous (ecallantide SQ): at least eight years.
    6. Haegarda intravenous (C1 Inhibitor Human IV), at least six years.
    7. Orladeyo oral (berotralstat): at least twelve years.
    8. Takhzyro SQ (lanadelumab – flyo): t least six years
  - B. Prescriber: allergist, immunologist, or hematologist.

C. Diagnosis and severity [must meet both listed below]:

1. Lab test [must meet both listed below]:

- a. C4: below 14mg/L (normal 9 - 36 mg/dL) or below fifty percent at baseline.
- b. C1 Inhibitor (antigenic) below 19.9mg/dL (normal 21 - 39mg/dL) or C1 Inhibitor functional below 72% reference range (normal above 67% reference range).

2. Concomitant medications: medications known to cause angioedema (i.e., ACE inhibitors, estrogens, ARBs) have been evaluated and discontinued when appropriate.

II. Acute Hereditary Angioedema treatment [must meet all listed below]:

A. Administration [must meet one listed below]:

1. Self-administration: Berinert, Firazyr and Ruconest after training by health care professional.
2. Health care professional administration: Kalbitor (due to high risk of anaphylaxis).

B. Dosage regimen:

1. Berinert intravenous (plasma derived C1 INH IV):

- a. Children and adolescents: 15 to 30 units per Kg on demand or within 6 hours prior to procedure.
- b. Adults: 20 units per Kg on demand or within six hours of procedure.

2. Ruconest Intravenous (recombinant C1 INH IV):

- a. Below 84 Kg: 50 units per Kg, may repeat times one.
- b. At or above 84 Kg: 4,200 units; may repeat times one.

3. Kalbitor subcutaneous (ecallantide SQ): adult and pediatric 30mg (3 times 1mL).

4. Firazyr subcutaneous (icatibant SQ):

- a. Adult: 30mg.
- b. Pediatric: 0.4mg per Kg (maximum 30mg).

C. Approval:

- a. Initial: six months.
- b. Re-approval: one year; quantity dependent on frequency of attacks (decreased severity and duration of attacks).

III. Prophylactic Hereditary Angioedema treatment.

A. Diagnosis and severity [must meet one listed below]:

1. Frequent and severe HAE attacks: at least 24 days per year with symptoms or at least 12 severe attacks per year.
  2. Severe HAE attacks in triggering situations: major dental work, surgical procedures, or invasive medical procedures.
- B. Concomitant therapies: acute hereditary angioedema agents to be available for on demand treatment in conjunction with prophylactic agent.
- C. Dosage regimen.
1. Cinryz intravenous (C1 Inhibitor Human IV):
    - a. Children at or above six to 11 years: 500 units every three to four days or within 24 hours of procedure.
    - b. Adults and adolescents: 1,000 units every three to four days or within 24 hours of procedure.
  2. Haegarda subcutaneous (C1 Inhibitor Human SQ): children and adults, 40 to 60 units per Kg every three to four days.
  3. Takhzyro subcutaneous (lanadelumab-flyo SQ): 300mg every two weeks.
  4. Orladeyo oral (berotralstat):
    - a. 150mg taken orally once daily with food.
    - b. Hepatic impairment or concomitant use with P-gp or BCRP inhibitors: daily dose must be reduced to 110mg.
- D. Approval:
1. Initial: six months.
    - a. Re-approval: one year (functional improvement with decreased frequency, severity, and duration of attacks).

IV. Appropriate medication use [must meet all listed below]:

- A. Diagnosis: meets standard diagnostic criteria that designates signs, symptoms, and test results to support specific diagnosis.
- B. Food and Drug Administration (FDA) approval status [must meet one listed below]:
  1. FDA approved: product, indication, and/or dosage regimen.
  2. Non-FDA approved: compendium support (Lexi comp™) for use of a drug for a non- FDA approved indication or dosage regimen.
- C. Place in therapy: sequence of therapy supported by national or international accepted guidelines and/or studies (e.g., oncologic, infectious conditions).

**4.0 Coding:**

|                       |
|-----------------------|
| <b>AFFECTED CODES</b> |
|-----------------------|

| Code  | Brand Name | Generic Name             | Billing Units (1U) | Prior Approval |
|-------|------------|--------------------------|--------------------|----------------|
| J0598 | Cinryze    | C1 Inhibitor Human       | 10U                | Y              |
| J0597 | Beriner    | C1 Inhibitor Human       | 10U                | Y              |
| J1290 | Kalbitor   | escallantide             | 1mg                | Y              |
| J1744 | Firazyr    | icatibant                | 1mg                | Y              |
| J0599 | Haegarda   | C1 Inhibitor Human       | 10U                | Y              |
| J0596 | Ruconest   | C1 Inhibitor recombinant | 10U                | Y              |
| J0593 | Takhzyro   | lanadelumab              |                    | Y              |

### 5.0 References, Citations & Resources:

1. Lexi comp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Beriner, Cinryze, Haegarda; Firazy; Ruconest, Kalbitor, Takhzyro, Orladeyo accessed October 2021.
2. Hereditary angioedema: a current state-of-the-art review VII: Canadian Hungarian 2007 Consensus Algorithm for the diagnosis, therapy, and management of Hereditary Angioedema. *Ann Allergy Asthma Immunol* 2008; 100(suppl 2):S30-S40 &S41-S46.
3. Hereditary angioedema: a current state-of-the art review, II; historical perspective of non-histamine-induced angioedema. *Drugs* 2008; 68(18):2561-2573.
4. Treatment of Hereditary angioedema: current perspectives. *Recent Patents on Inflammation & Allergy Drug, Discovery* 2008; 2(3):166-174.
5. When is prophylaxis for hereditary angioedema necessary? *Ann Allergy Asthma Immunol.* 2009; 102:366-372.
6. Recurrent Angioedema & the treat of asphyxiation. *Ann Allergy Asthma Immunol.* 2008; 100:153-161. C-1 Inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. *Transfusion* 2009;9:1987-1995.
7. HAE therapies: past, present, and future. *J Allergy Clin Immunol* 2004;14(3):629-637.
8. A focused parameter update: Hereditary angioedema, acquired C1 deficiency, & angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol*:131(6);1491-93.e25.
9. Review of recent guidelines and consensus statements on hereditary angioedema therapy with focus on self-administration *Int Arch Allergy Immunol.* 2013; 16 (suppl 1):3-9.
10. Update on the treatment of hereditary angioedema. *Clinical & Experimental Allergy.*2013; 43:395-405.
11. Hereditary angioedema: General and long-term prophylaxis. UpToDate. Waltham, MA: UpTo Date Inc. accessed August 2017.
12. US Hereditary Angioedema Association Medical Advisory Board 2013 Recommendations For The Management Of Hereditary Angioedema Due To C1 Inhibitor Deficiency, *J allergy Clin Immunol Practice* 2013;1:458.
13. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract.* 2021;9(1):132-150.e3. doi:10.1016/j.jaip.2020.08.046[[PubMed 32898710](https://pubmed.ncbi.nlm.nih.gov/32898710/)]

### 6.0 Appendices:

See page 6.

### 7.0 Revision History:

Original Effective Date: 10/28/2010

Next Review Date: 11/10/2023

| Revision Date | Reason for Revision  |
|---------------|--|
| 7/19          | Moved to new format  |
| 10/20         | Annual review, updated age for use of products, clarified criteria instructions, revised other therapies language, replaced abbreviations, approved by P&T Committee 12/9/20 |
| 3/21          | Off cycle review, added drug Orladeyo, clarified C1 inhibitor protein level  |
| 9/21          | Added code for Tekhzyro  |
| 10/21         | Annual review: revised ages and doses for products, removed severity statement   |

| Revision Date | Reason for Revision   |
|---------------|---|
|               | from IC, removed androgens as other therapies for prophylaxis |
| 10/22         | Annual review, added reference                                |

Appendix I: Monitoring & Patient Safety

| Drug  | Adverse Reactions   | Monitoring   | REMS       |
|---|---|--|------------|
| Berinert IV<br>Cinryze IV<br>Haegarda SQ<br>plasma C1-INH | <ul style="list-style-type: none"> <li>• Central Nervous System : headache (17%)</li> <li>• Gastrointestinal: nausea (18%)</li> <li>• Pregnancy: animal reproductive studies have not been conducted</li> </ul>   | <ul style="list-style-type: none"> <li>• Cardiovascular: signs and symptoms thrombolytic events</li> <li>• Immunologic: signs and symptoms of hypersensitivity.</li> </ul>     | Not needed |
| Kalbitor SQ<br>ecallantide                                | <ul style="list-style-type: none"> <li>• Central Nervous System: headache (8-16%), fatigue (12%)</li> <li>• Gastrointestinal: nausea (5-13%), diarrhea (4-11%)</li> <li>• Immunologic: antibody development (IgE: 5-20%, neutralizing: 9%)</li> <li>• Pregnancy: adverse effects were observed in animal studies</li> </ul> | <ul style="list-style-type: none"> <li>• Immunologic: signs and symptoms of hypersensitivity</li> </ul>  | Not needed |
| Takhzyro SQ<br>lanadelumab-flyo                           | <ul style="list-style-type: none"> <li>• Central Nervous System: headache (33%)</li> <li>• Immunologic: antibody development (12%)</li> <li>• Local: injection site reaction (45-56%)</li> <li>• Musculoskeletal: myalgia (11%)</li> <li>• Respiratory: upper respiratory infection (44%)</li> </ul>                        | <ul style="list-style-type: none"> <li>• NA</li> </ul>   | Not needed |
| Firazyr SQ<br>icatibant                                   | <ul style="list-style-type: none"> <li>• Dermatology: injection site reaction (97%),</li> <li>• Pregnancy: adverse effects were observed in animal studies</li> </ul>   | <ul style="list-style-type: none"> <li>• Symptoms: relief laryngeal symptoms or airway obstruction</li> </ul>  | Not needed |
| Ruconest IV<br>recombinant C1 INH                         | <ul style="list-style-type: none"> <li>• Central Nervous System: headache (&gt;10%)</li> <li>• Gastrointestinal: abdominal pain (≥12%)</li> <li>• Respiratory: oropharyngeal (≥12%)</li> </ul>  | <ul style="list-style-type: none"> <li>• Cardiovascular: signs and symptoms of thrombolytic events</li> <li>• Miscellaneous: signs and symptoms of hypersensitivity</li> </ul> | Not Needed |
| Orladeyo oral<br>berotralstat                             | <ul style="list-style-type: none"> <li>• Gastrointestinal: abdominal pain (10-23%), diarrhea (10-15%), vomiting (10-15%)</li> </ul>   | <ul style="list-style-type: none"> <li>• NA</li> </ul>   | Not needed |