DRUG DETERMINATION POLICY

Title: DDP-30 Hereditary Angioedema Agents

Effective Date: 06/01/2021

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 (HAE).

A. Age:

1. Ruconest intravenous (C1 estrase Inhibitor, recombinant IV): adolescents and adults.

2. Firazyr subcutaneous (icatibant SQ): at least two years.

3. Berinert intravenous (C1 Estrase Inhibitor Human IV): at least five years.

4. Cinryz intravenous (C1 Inhibitor Human IV): at least six years.

5. Kalbitor subcutaneous (ecallantide SQ): at least eight years.

6. Haegarda intravenous (C1 Inhibitor Human IV), Takhzyro subcutaneous (lanadelumab-flyo SQ): at least twelve years.

7. Orladeyo oral (berotralstat): at least twelve years.

B. Prescriber: allergist, immunologist or hematologist.

C. Diagnosis and severity [must meet all 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. Severity: swelling of face and/or throat or GI tract that notably interferes with routine daily activities.

3. 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.

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.

B. Dosage regimen:

1. Berinert intravenous (plasma-derived C1 INH IV): 20 units per Kg.

2. Ruconest Intravenous (recombinant C1 INH IV): below 84 Kg - 50 units per Kg, 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): adult - 30mg; 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. Other therapies: contraindicated, inadequate response or significant adverse effects from one listed below:

1. Acute Hereditary Angioedema treatment (see II).

2. Attenuated androgens: danazol, stanozolol.

C. Dosage regimen.

1. Cinryz intravenous (C1 Inhibitor Human IV): at or above six to 11 years - 500 units every three to four days; at least 12 years - 1,000 units every three to four days.

2. Haegarda subcutaneous (C1 Inhibitor Human SQ): 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. Off-label use: at least two supporting studies from major peer-reviewed medical journals that support the off-label use as safe and effective.

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:

AFFECTED CODES				
Code	**Brand Name**	**Generic Name**	**Billing Units (1U)**	**Prior Approval**
J0598	Cinryze	C1 Inhibitor Human	10U	Y
J0597	Berinert	C1 Inhibitor Human	10U	Y

AFFECTED CODES				
Code	**Brand Name**	**Generic Name**	**Billing Units (1U)**	**Prior Approval**
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. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Berinert, Cinryze, Haegarda; Firayz; Ruconest, Kalbitor, Takhzyro, Orladeyo accessed April 2020.
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, Jallergy Clin Immunol Practice 2013;1:458.

6.0 Appendices:

See page 5.

7.0 Revision History:

Original Effective Date: 10/28/2010

Next Review Date: 11/10/2021

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

Appendix I: Monitoring & Patient Safety

Drug	Adverse Reactions	Monitoring	REMS
Berinert IV Cinryze IV Haegarda SQ plasma C1-INH	• Central Nervous System : headache (17%) • Gastrointestinal: nausea (18%) • Pregnancy: animal reproductive studies have not been conducted	• Cardiovascular: signs and symptoms thrombolyic events • Immunologic: signs and symptoms of hypersensitivity.	Not needed
Kalbitor SQ ecallantide	• Central Nervous System: headache (8-16%), fatigue (12%) • Gastrointestinal: nausea (5-13%), diarrhea (4-11%) • Immunologic: antibody development (IgE: 5-20%, neutralizing: 9%) • Pregnancy: adverse effects were observed in animal studies	• Immunologic: signs and symptoms of hypersensitivity	Not needed
Takhzyro SQ lanadelumab-flyo	• Central Nervous System: headache (33%) • Immunologic: antibody development (12%) • Local: injection site reaction (45-56%) • Musculoskeletal: myalgia (11%) • Respiratory: upper respiratory infection (44%)	• NA	Not needed
Firazyr SQ icatibant	• Dermatology: injection site reaction (97%), • Pregnancy: adverse effects were observed in animal studies	• Symptoms: relief laryngeal symptoms or airway obstruction	Not needed
Ruconest IV recombinant C1 INH	• Central Nervous System: headache (>10%) • Gastrointestinal: abdominal pain (≥12%) • Respiratory: oropharyngeal (≥12%)	• Cardiovascular: signs and symptoms of thrombolyic events • Miscellaneous: signs and symptoms of hypersensitivity	Not Needed
Orladeyo oral berotralstat	• Gastrointestinal: abdominal pain (10-23%), diarrhea (10-15%), vomiting (10-15%)	• NA	Not needed