DRUG DETERMINATION POLICY

Title: DDP-30 Hereditary Angioedema Agents

Effective Date: 08/14/2019

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:

A. Hereditary Angioedema (HAE).

1. Age:

   a. Berinert IV (C1 Estrase Inhibitor Human), Cinryz IV (C1 Inhibitor Human), Haegarda SC (C1 Inhibitor Human), Ruconest IV (C1 estrase Inhibitor, recombinant):: adolescents and adults.

   b Firazyr SC (icatibant): at least two years.

   c. Kalbitor SC (ecallantide): at least eight years.

   d. Haegarda IV (C1 Inhibitor Human), Takhzyro SC (lanadelumab-flyo): at least twelve years

2. Prescriber: allergist, immunologist or hematologist.

3. Diagnosis and severity.

    a. Lab test (both below)

        i. C4: <14mg/L (normal 9 - 36 mg/dL).

        ii. C1 Inhibitor (antigenic) <19.9mg/dL (normal 21 - 39mg/dL) or C1 Inhibitor (functional<72% reference range (normal >67% reference range).

    b. Severity: swelling of face and/or throat or GI tract that notably interferes with routine daily activities.

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

B. Acute HAE treatment.

1. Administration:

    a. Self-administration: Berinert, Firazyr and Ruconest after training by health care professional.

    b. Health care professional administration: Kalbitor.

2. Dosage regimen:

    a. Berinert IV (plasma-derived C1 INH): 20U/Kg.

    b. Ruconest IV (recombinant C1 INH): < 84 Kg: 50 U/KG, ≥ 84 Kg: 4,200 U; may repeat times one.

    c. Kalbitor SC (ecallantide): adult and pediatric- 30mg (3 x 1mL).

    d. Firazyr SC (icatibant): adult - 30mg; pediatric - 0.4mg/Kg (maximum 30mg).

3. Approval:

    a. Initial: six months.

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

C. Prophylactic HAE treatment.

1. Diagnosis and severity:

    a. Frequent and severe HAE attacks: at least 24 days per year with symptoms or at least12 severe attacks per year.

    b. Severe HAE attacks in triggering situations: major dental work, surgical procedures or invasive medical procedures.

2. Other therapies: failed or contraindication/significant adverse effects from one below:

    a. Acute HAE treatment (see B).

b. Attenuated androgens: danazol, stanozolol.

3. Dosage regimen.

   a. Cinryz IV (C1 Inhibitor Human): 12 years and up - 1,000U every three to four days; 6-11 years – 500U every three to four days.

   b. Haegarda SC (C1 Inhibitor Human): 60U/Kg every three to four days.

   c. Takhzyro SC (lanadelumab-flyo): 300mg every two weeks.

4. Approval:

   a. Initial: six months.

   b. Re-approval: one year (functional improvement with decreased frequency, severity and duration of attacks).

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
J1290	Kalbitor	escallantide	1mg	Y
J1744	Firazyr	icatibant	1mg	Y
J0599	Haegarda	C1 Inhibitor Human	10U	Y
J0596	Ruconest	C1 Inhibitor recombinant	10U	Y
Pending	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 accessed July 2019.

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:

Appendix I: Monitoring & Patient Safety

Drug	Adverse Reactions	Monitoring	REMS
Berinert IV Cinryze IV Haegarda SC plasma C1-INH	• Central Nervous System (CNS) : headache (HA) (17%) • Gastro Intestinal (GI): nausea (18%) • Pregnancy: animal reproductive studies have not been conducted	• CV: Signs & Symptoms (S & Sx) thrombolyic events • Immunologic: S & Sx hypersensitivity.	Not needed
Kalbitor ecallantide	• CNS: HA (8-16%), fatigue (12%) • GI: nausea (5-13%), diarrhea (4-11%) • Immunologic: antibody development (IgE: 5-20%, neutralizing: 9%) • Pregnancy: adverse effects were observed in animal studies	• Immunologic: S & Sx hypersensitivity	REMS program Dc'ed by FDA April 2013
Takhzyro SC lanadelumab-flyo	• CNS: HA (33%) • Immunologic: antibody development (12%) • Local: injection site reaction (45-56%) • Musculoskeletal: myalgia (11%) • Respiratory: URI (44%)	• NA	Not needed
Firazyr SC icatibant	• Dermatology: inj. site Rx (97%), • Pregnancy: adverse effects were observed in animal studies	• Symptoms relief laryngeal sx/airway obstruction	Not needed
Ruconest IV recombinant C1 INH	• CNS: HA (>10%) • GI: abdominal pain (≥12%) • Respiratory: oropharyngeal (≥12%)	• CV: S & Sx thrombolyic events • Misc: S & Sx hypersensitivity	Not Needed

7.0 Revision History:

Original Effective Date: 10/28/2010

Next Review Date: 08/14/2020

Revision Date	Reason for Revision
7/19	Moved to new format