Pharmacy Policy Bulletin

Title: Hereditary Angioedema Agents

Policy #: Rx.01.109

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

Intent:

The intent of this policy is to communicate the medical necessity criteria for **Takhzyro® (lanadelumab-flyo), Haegarda® (C1 esterase inhibitor subcutaneous [human]), Cinryze® (C1 esterase inhibitor [human]), Berinert® (C1 esterase inhibitor [human]), Ruconest® (C1 inhibitor recombinant), Sajazir™/Firazyr®** (i**catibant**), **and Orladeyo™ (berotralstat)** as provided under the member's pharmacy benefit.

Description:

Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent episodes of angioedema. The most frequently implicated areas during an attack of HAE include areas of the skin, gastrointestinal tract, and upper respiratory tract, including the larynx. Involvement of the larynx may lead to fatality by asphyxiation. During episodes of HAE, individuals experience severe edema of the affected areas, characterized by gradual worsening over 24 hours and resolution within 2-5 days without treatment. Importantly, symptoms of HAE exclude urticaria and pruritis.

Several forms of hereditary angioedema exist, with type I and II being most common. In most cases, individuals with HAE demonstrate a deficiency in C1 inhibitor caused by mutation in the C1 inhibitor gene. .

Neither anabolic steroids nor antifibrinolytic drugs, used for prophylaxis of HAE attacks, are reliably effective in treating acute HAE attacks. Epinephrine, corticosteroids, and antihistamines are also not effective for treating HAE attacks and are not recommended by current guidelines. Guidelines recommend that patients with HAE have access to an "effective, on-demand, HAE-specific agent" to manage acute attacks.

Mechanism of Action

Vasodilation results from excessive bradykinin production, a downstream effect from a deficiency in C1 (a subset of Complement protein) inhibitor protein. C1-inhibitor protein inhibits kallikrein, which is a protease that activates the potent vasodilator, bradykinin. Modulation of the C1 cascade is a target for the prophylaxis and treatment of acute attacks of HAE. Patients with HAE have low levels of endogenous or functional C1 esterase inhibitor (C1INH). Although the events that induce attacks of angioedema in HAE patients are not well understood, it is thought that contact system activation occurs. Contact system activation results in increased levels of bradykinin which causes increases in vascular permeability which results in the clinical manifestations of HAE.

Sajazir™/Firazyr® (icatibant) inhibits bradykinin from binding the B2 receptor and thereby treats the clinical symptoms of an acute, episodic attack of hereditary angioedema. Icatibant is a bradykinin B2 receptor antagonist indicated for treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older.

Haegarda® (C1 esterase inhibitor subcutaneous [human]) is a plasma-derived concentrate of C1 esterase inhibitor (human) that is indicated for routine prophylaxis to prevent HAE attacks in patients 6 years of age and older.

Cinryze® (C1 esterase inhibitor [human]) is C1 esterase inhibitor indicated for routine prophylaxis against angioedema attacks in pediatric (6 years old and above), adolescent and adult patients with HAE.

Berinert® (C1 esterase inhibitor [human] is a plasma-derived C1 esterase inhibitor (human) indicated for the treatment of acute abdominal, facial, or laryngeal HAE attacks in adult and pediatric patients.

Orladeyo™ (berotralstat) is a plasma kallikrein inhibitor indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older.

Ruconest® is a C1 esterase inhibitor [recombinant] indicated for the treatment of acute attacks in adults and adolescent patients with HAE.

Takhzyro® (lanadelumab-flyo) is a human monoclonal antibody that acts to inhibit plasma kallikrein, and is indicated for prevention of HAE in patients 12 years of age and older. Kallikrein is a protease that activates bradykinin, a potent vasodilator implicated in the pathogenesis of angioedema attacks in patients with HAE. Inhibition of kallikrein results in downstream inhibition of bradykinin production.

Policy:

Prophylaxis against angioedema attacks

INITIAL CRITERIA: C1 esterase inhibitor (human) (Cinryze® or Haegarda®) is approved when ALL of the following are met:

1. Diagnosis of hereditary angioedema (HAE) is confirmed by decreased serum levels of C4 and absence or marked decrease (less than 50 percent of normal) of the level or function of C1-INH; and
2. Prescribed by or in consultation with an immunologist, allergist, or pulmonologist; and
3. Member is 6 years of age or greater

Initial authorization duration: 2 years

REAUTHORIZATION CRITERIA CI esterase inhibitors (human) (Cinryze® or Haegarda®) is re-approved with documentation of positive clinical response to therapy.

Reauthorization duration: 2 years

INITIAL CRITERIA: Lanadelumab-flyo (Takhzyro®) injection or berotralstat (Orladeyo®**)** is approved when all of the following are met:

1. Diagnosis of hereditary angioedema (HAE); and
2. Member is 12 years of age or older; and
3. Prescribed by or in consultation with an immunologist, allergist, or pulmonologist

Initial authorization duration: 2 years

REAUTHORIZATION CRITERIA: Lanadelumab-flyo (Takhzyro®), or berotralstat (Orladeyo®) is re-approved with documentation of positive clinical response to therapy.

Reauthorization duration: 2 years

Treatment of angioedema attacks

INITIAL CRITERIA: C1 esterase inhibitor (human) (Berinert®) is approved when ALL of the following are met:

1. Diagnosis of treatment of acute abdominal, facial, or laryngeal attacks of HAE in adults and pediatric patients; and
2. Prescribed by or in consultation with an immunologist, allergist, or pulmonologist; and

3. One of the following:
    a. Inadequate response or inability to tolerate C1 esterase inhibitor recombinant (Ruconest®); or
    b. One of the following:
        i. Member is 12 years of age or younger; or
        ii. Documentation that member has history of laryngeal attacks

Initial authorization duration: 2 years

REAUTHORIZATION CRITERIA C1 esterase inhibitors (human) (Berinert®) is re-approved with documentation of positive clinical response to therapy.

Reauthorization duration: 2 years

INITIAL CRITERIA: C1 esterase inhibitor recombinant (Ruconest®) is approved when ALL of the following are met:

1. Diagnosis of treatment of acute attacks of HAE in adults and adolescents over the age of 12 years; and
2. Prescribed by or in consultation with an immunologist, allergist, or pulmonologist.

Initial authorization duration: 2 years

REAUTHORIZATION CRITERIA C1 esterase inhibitor recombinant (Ruconest®) is re-approved with documentation of positive clinical response to therapy.

Reauthorization duration: 2 years

INITIAL CRITERIA: Icatibant (Firazyr® /Sajazir™) is approved when ALL of the following are met:

1. Member is 18 years of age or older; and
2. Diagnosis of hereditary angioedema; and
3. Prescribed by or in consultation with an immunologist, allergist, or pulmonologist

Initial authorization duration: 2 years

REAUTHORIZATION CRITERIA Icatibant (Firazyr®/Sajazir™) is re-approved with documentation of positive clinical response to therapy.

Reauthorization duration: 2 years

Black Box Warning as shown in the drug Prescribing Information:

None

Guidelines:

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

References:

Firazyr® (icatibant) [package insert]. Lexinton MA. Shire Orphan Therapeutics. Oct, 2021 Available at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=ed6657ca-ab68-477a-9968-e12dc928b540&type=display. Accessed August 10, 2022

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Haegarda® (C1 esterase inhibitor subcutaneous [human]). [package insert]. Kanakee, IL: CSL Behring. January 2022. Available at: http://labeling.cslbehring.com/PI/US/HAEGARDA/EN/HAEGARDA-Prescribing-Information.pdf. Accessed August 10, 2022.

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Orladeyo™ (berotralstat). [prescribing information]. Durham, NC: BioCryst Pharmaceuticals, Inc. March 2022. Available at: https://orladeyohcp.com/wp-content/uploads/ORLADEYO_PI_V1_2020.pdf. Accessed August 10, 2022.

Ruconest® (C1 esterase inhibitor [recombinant]). [package insert]. Raleigh, NC: Santarus, Inc. April 2020. Available at: https://www.ruconest.com/PDF/ruconest-pi.pdf. Accessed August 10, 2022

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Takhzyro®. [package insert]. Lexington, MA: Dyax Corp., wholly-owned subsidiary of Shire US Inc. November 2018. Available at: https://www.shirecontent.com/PI/PDFs/TAKHZYRO_USA_ENG.pdf. Accessed August 10, 2022.

Cicardi MD, Zuraw, MD. Hereditary angioedema: Pathogenesis and diagnosis. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com/contents/hereditary-angioedema-pathogenesis-and-diagnosis?search=Hereditary%20angioedema:%20Pathogenesis%20and%20diagnosis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.Accessed on August 10, 2022

Applicable Drugs:

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Brand Name	Generic Name
Firazyr®/**Sajazir™**	icatibant
Haegarda®	C1 esterase inhibitor subcutaneous [human]
Cinryze®	C1 esterase inhibitor [human]
Berinert®	C1 esterase inhibitor [human]
Orladeyo™	berotralstat
Ruconest®	C1 esterase inhibitor [recombinant]
Takhzyro®	lanadelumab-flyo

Cross References:

Rx.01.33 Off Label Use

Rx.01.76 Quantity Level Limits for Pharmaceuticals Covered Under the Prescription Drug Benefit

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The Policy Bulletins on this web site were developed to assist the Company in administering the provisions of the respective benefit programs, and do not constitute a contract. If you have coverage through the Company, please refer to your specific benefit program for the terms, conditions, limitations and exclusions of your coverage. Company does not provide health care services, medical advice or treatment, or guarantee the outcome or results of any medical services/treatments. The facility and professional providers are responsible for providing medical advice and treatment. Facility and professional providers are independent contractors and are not employees or agents of the Company. If you have a specific medical condition, please consult with your doctor. The Company reserves the right at any time to change or update its Policy Bulletins.