Washington State Health Care Authority

Hematological Agents: Hereditary Angioedema Agents – Acute

Medical policy no. 85.82.00.AA-1 Effective Date: 4/1/2024

Related medical policies:

Policy Name	Indications
85.80.20.AA- Hematological Agents: Hereditary Angioedema Agents- Prophylaxis	Treatment of hereditary angioedema, prophylaxis

Note: *New-to-market drugs included in this class based on the Apple Health Preferred Drug List are non-preferred and subject to this prior authorization (PA) criteria. Non-preferred agents in this class require an inadequate response or documented intolerance due to severe adverse reaction or contraindication to at least TWO preferred agents. If there is only one preferred agent in the class documentation of inadequate response to ONE preferred agent is needed. If a drug within this policy receives a new indication approved by the Food and Drug Administration (FDA), medical necessity for the new indication will be determined on a case-by-case basis following FDA labeling.*

To see the list of the current Apple Health Preferred Drug List (AHPDL), please visit: https://www.hca.wa.gov/assets/billers-and-providers/apple-health-preferred-drug-list.xlsx

Medical necessity

Drug	Medical Necessity
C1 Esterase Inhibitor (Human) (Berinert) C1 Esterase Inhibitor (Recombinant) (Ruconest) Ecallantide (Kalbitor) Icatibant Acetate (Firazyr, Sajazir)	**Hereditary Angioedema Agents- Acute** may be considered medically necessary in patients who meet the criteria described in the clinical policy below. If all criteria are not met, the clinical reviewer may determine there is a medically necessary need and approve on a case-by-case basis. The clinical reviewer may choose to use the reauthorization criteria when a patient has been previously established on therapy and is new to Apple Health.

Clinical policy:

Clinical Criteria	
Acute Attacks C1 Esterase Inhibitor [Human] (Berinert) C1 Esterase Inhibitor [Recombinant] (Ruconest) Ecallantide (Kalbitor) Icatibant Acetate (Firazyr, Sajazir)	C1 Esterase Inhibitor [Human] (Berinert) may be approved when all the following criteria are met: 1. Patient is 5 years of age or older; **AND** 2. Prescribed by, or in consultation with a specialist (e.g. allergist, immunologist, pulmonologist, hematologist) who specializes in the treatment of hereditary angioedema (HAE); **AND** **3.** Patient is not prescribed more than one agent that treats acute HAE attacks; **AND** 4. Diagnosis of HAE with documentation supporting one of the following:

	For HAE-1: i. C1-INH function- low; **AND** ii. C1-INH protein- low; **AND** iii. C4-low; **OR** For HAE-2: iv. C1-INH function- low; **AND** v. C1-INH protein- normal or elevated; **AND** vi. C4-low; **AND** 5. Provider attests that the patient has been evaluated for triggers that may induce attacks and is being managed to avoid triggers C1 Esterase Inhibitor [Recombinant] (Ruconest) may be approved when all the following criteria are met: 6. Criteria 2-5 is met; **AND** 7. Treatment with two Preferred Apple Health Preferred Drug List (PDL) medications has been ineffective, contraindicated, or not tolerated; **AND** 8. Patient is 13 years of age or older Ecallantide (Kalbitor) may be approved when all the following criteria are met: 9. Criteria 2-5 is met; **AND** 10. Patient is 12 years of age or older Icatibant Acetate (Firazyr, Sajazir) may be approved when all the following criteria are met: 11. Criteria 2-5 is met; **AND** 12. Patient is 18 years of age or older If ALL criteria are met, the request will be authorized for **12 months.**
	Criteria (Reauthorization) C1 Esterase Inhibitor [Human] (Berinert), C1 Esterase Inhibitor [Recombinant] (Ruconest), Ecallantide (Kalbitor), and Icatibant Acetate (Firazyr, Sajazir) may be approved when all of the following criteria are met: 1. Not used in combination with other products indicated for the treatment of acute HAE attacks; **AND** 2. Documentation is submitted demonstrating disease stability or a positive clinical response [e.g., the medication resolves acute attacks]. If ALL criteria are met, the request will be authorized for **12 months.**

Dosage and quantity limits

Drug	Indication	FDA Approved Dosing	Dosage Form
C1 Esterase Inhibitor [Human] (Berinert)	Acute abdominal, facial, or laryngeal hereditary angioedema attacks	20 IU/kg intravenously	• 500 IU injection kit
C1 Esterase Inhibitor [Recombinant] (Ruconest)	Acute attacks	50 IU/kg intravenously, may repeat if symptoms persist. Max dose= 8400 IU/24 hrs	• 2100 IU/vial
Ecallantide (Kalbitor)	Acute attacks	30 mg subQ in three 10-mg injections; an additional dose of 30 mg may be administered within a 24 hr period if attack persists	• 10 mg/1 mL vial
Icatibant Acetate (generic)	Acute attacks	30 mg subQ into the abdominal area; additional doses of 30 mg may be administered at intervals of at least 6 hrs if attack persists or symptoms recur. Max= 3 doses in 24 hours	• 30 mg/3 mL prefilled syringe
Icatibant Acetate (Firazyr)	Acute attacks	30 mg subQ into the abdominal area; additional doses of 30 mg may be administered at intervals of at least 6 hrs if attack persists or symptoms recur. Max= 3 doses in 24 hours	• 30 mg/3 mL prefilled syringe
Icatibant Acetate (Sajazir)	Acute attacks	30 mg subQ into the abdominal area; additional doses of 30 mg may be administered at intervals of at least 6 hrs if attack persists or symptoms recur. Max= 3 doses in 24 hours	• 30 mg/3 mL prefilled syringe

Coding:

HCPCS Code	Description
J0597	Injection, C-1 esterase inhibitor (human), berinert, 10 units
J0596	Injection, C-1 esterase inhibitor (recombinant), ruconest, 10 units
J1290	Injection, ecallantide, 1 mg
J1744	Injection, icatibant, 1 mg

Background:

Hereditary Angioedema (HAE) is a rare disease characterized by recurrent attacks of severe swelling of the skin and mucous membranes. Swelling typically occurs in the hands, feet, limbs, face, intestinal tract, or airway. Emotional stress, physical stress, and dental procedures are the most common triggers, however various triggers of attacks can occur. There are two common forms of HAE, Type I and Type II. Both forms may be managed with acute and prophylaxis treatment depending on severity, attack frequency and drug tolerability. The International World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) guidelines recommend intravenous C1-Esterase, ecallanatide, or icatibant as first-line treatment options for acute attacks.

FDA approval of Berinert was based on the IMPACT-1 trial which was a prospective, multi-national, randomized, double-blind, placebo-controlled, parallel-group, dose-find, three-arm clinical study. 124 adult and pediatric patients with Type I or II HAE experienced an acute moderate to severe abdominal or facial HAE attack were treated with Berinert or placebo. Patients were randomized to receive a single dose of Berinert 10U/kg, Berinert 20U/kg, or placebo by slow IV injection within five hours of an attack. The primary study outcomes were comparing time to onset of relief of symptoms of an abdominal or facial attack with Berinert compared to placebo and to compare two different dosing regimens of Berinert for efficacy. Patients treated with 20U/kg of Berinert experienced a significant decrease in time to onset of relief of symptoms of HAE attack compared to placebo with a median of 30 minutes for Berinert 20U/kg vs. 1.5 hours for placebo (p=0.0025). There was no statistically significant difference in time to onset of symptom relief in the 10U/kg Berinert group compared to placebo (p=0.273). Onset of symptom relief within 60 minutes was achieved in more than 75% and approximately 40% of patients in the Berinert 20U/kg gnd placebo groups, respectively, and median time to complete resolution of HAE symptoms was 4.9 hours and 7.8 hours, respectively.

FDA approval of Kalbitor was based on results of the EDEMA3 and EDEMA4 clinical trials. EDEMA3 was a randomized, double-blind, placebo-controlled trial which enrolled 72 patients. Patients were randomized to receive Kalbitor or placebo for acute attacks of HAE. The primary endpoint evaluated was Treatment Outcome Score (TOS) at four hours and the key secondary efficacy endpoint was change from baseline in Mean Symptom Complex Severity (MSCS) at four hours. Kalbitor demonstrated a greater decrease from baseline in MSCS (p=0.041) than placebo and a greater TOS (p=0.045) than patients treated with placebo. EDEMA4 was also a randomized, double-blind, placebo-controlled trial which enrolled 96 patients. Patients were randomized to receive Kalbitor 30 mg subQ or placebo for acute HAE attacks. The same primary and secondary endpoints of MSCS and TOS at four hours were evaluated. Results from the study showed that patients treated with Kalbitor demonstrated a greater decrease from baseline in MSCS (p=0.010) than placebo and a greater TOS (p=0.003) than patients with placebo. In both clinical trials, patients in the placebo group required medical intervention to treat unresolved symptoms within 24 hours compared to the Kalbitor treated group.

The “For Angioedema Subcutaneous treatment” (FAST-1 and FAST-2) trials were the basis of approval for Firazyr. The FAST-1 and FAST-2 trials were randomized, multicenter, phase III trials where 130 adults with C1-INH deficiency were treated with icatibant for moderate-to-severe laryngeal, gastrointestinal, or cutaneous attacks. FAST-1 compared icatibant with placebo and FAST-2 compared icatibant with tranexamic acid. The primary endpoint for both trials was time to onset of symptom relief. FAST-1 did not demonstrate a clear benefit of icatibant over placebo, but FAST-2 did (2 hours with icatibant vs. 11 hours with tranexamic acid). In a pooled analysis of the two trials, significantly more patients receiving icatibant had symptom relief within four hours compared with placebo or tranexamic acid.

References

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History

Approved Date	Effective Date	Version	Action and Summary of Changes
10/18/2023	04/01/2024	85.82.00.AA-1	Approved by DUR Board -New policy created