

# Hereditary Angioedema

## Goal(s):

- To promote safe and effective use of hereditary angioedema treatments.

## Length of Authorization:

- Up to 12 months

## Requires PA:

- All pharmacotherapy for hereditary angioedema (pharmacy and physician administered claims).

NOTE: This policy does not apply to hereditary angioedema treatments administered during emergency department visits or hospitalization.

## Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

**Table 1.** FDA Approved indications and dosing for hereditary angioedema treatments

Drug Name	Place in Therapy	FDA Indication(s)	Dose and Frequency
<b>C1 esterase inhibitor (Berinert®)</b>	Acute	Abdominal, facial, or laryngeal attacks	20 units/kg intravenously as a single dose
<b>C1 esterase inhibitor, recombinant (Ruconest®)</b>	Acute	Attacks in adults and adolescents. Efficacy has not been established in laryngeal attacks.	50 units/kg intravenously as a single dose; maximum dose: 4,200 units; may repeat once within 24 hours if attack continues
<b>Ecallantide (Kalbitor®)</b>	Acute	Attacks in patients ≥12 years of age	30 mg as a one-time dose (3 subcutaneous injections); may repeat once within 24 hours if attack continues
<b>Icatibant (Firazyr®)</b>	Acute	Attacks in adults ≥18 years of age	30 mg injection once; may repeat every 6 hours if response is inadequate; maximum dose per day: 90 mg
<b>C1 esterase inhibitor (Cinryze®)</b>	Prophylaxis	HAE prophylaxis in patients ≥6 years of age	1,000 units intravenously every 3 to 4 days (twice weekly); doses up to 2,500 units (≤100 units/kg) every 3 or 4 days may be considered based on individual patient response.
<b>C1 esterase inhibitor (Haegarda®)</b>	Prophylaxis	HAE prophylaxis in patients ≥6 years of age	60 units/kg subcutaneous every 3 to 4 days (twice weekly)
<b>Berotralstat (Orladyo™)</b>	Prophylaxis	HAE prophylaxis in patients ≥12 years of age	110 mg or 150 mg orally daily
<b>Lanadelumab-flyo (Takhzyro™)</b>	Prophylaxis	HAE prophylaxis in patients ≥2 years of age	300 mg subcutaneous injection every 2 weeks (for ≥12 years) or 150 mg every 2 weeks (for 6-12 years); may consider dosing every 4 weeks for patients who are well-controlled for > 6 months; 150 mg every 4 weeks for 2-6 years of age

## Approval Criteria

1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of prophylactic therapy OR for treatment of a second acute attack previously approved through fee-for-service?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #3
3. Is the request for an FDA approved indication and place in therapy according to <b>Table 1</b> and is there confirmed laboratory diagnosis of hereditary angioedema (e.g., low C4 levels and either low C1 inhibitor antigenic levels or low C1 inhibitor functional levels)?	<b>Yes:</b> Go to #4  Document labs	<b>No:</b> Pass to RPh. Deny; medical appropriateness
4. Has the provider documented discussion with the patient of risks (including thrombotic events and/or anaphylaxis) versus benefits of therapy?	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; medical appropriateness.  Notify provider of potential serious adverse effects of therapy. See notes below.
5. Is the request for a C1 esterase inhibitor or ecallantide?	<b>Yes:</b> Go to #6	<b>No:</b> Go to #7
6. Is the patient prescribed concurrent epinephrine or do they have epinephrine on hand?	<b>Yes:</b> Go to #7	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
7. Is the medication intended to be administered by a non-healthcare professional (e.g., self-administered)?	<b>Yes:</b> Go to #8	<b>No:</b> Go to #9
8. Has the member received training on identification of an acute attack?	<b>Yes:</b> Go to #9	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
9. Is the request for treatment of an acute hereditary angioedema attack?	<b>Yes:</b> Go to #12  Document attack severity if available	<b>No:</b> Go to #10

Approval Criteria		
10. Is the request for prophylactic use in a patient with a history of hereditary angioedema attacks?	<b>Yes:</b> Go to #11  Document baseline number of attacks in the last 6 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
11. Have potential triggering factors for angioedema including medications such as estrogens, progestins, or angiotensin converting enzyme inhibitors been assessed and discontinued when appropriate?	<b>Yes:</b> Go to #12	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
12. Will the prescriber consider a change to a preferred product?  Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	<b>Yes:</b> Inform prescriber of covered alternatives in class.	<b>No:</b> Approve for the following recommended durations:  Acute treatment: Approve based on standard FDA dosing for treatment of a single acute attack (see <b>Table 1</b> )  Prophylactic treatment: Approve for up to 6 months or length of therapy, whichever is less.

Renewal Criteria		
1. Is the request for additional treatment for acute attacks?	<b>Yes:</b> Go to #2	<b>No:</b> Go to #5
2. Is there documented utilization and benefit of the initial approved dose?	<b>Yes:</b> Approve based on standard FDA dosing for treatment of a single acute attack (see <b>Table 1</b> ).  Document attack severity if available	<b>No:</b> Go to #3
3. Does the patient currently already have at least one on-demand dose for an acute attack?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #4

Renewal Criteria		
4. Is there documentation from the prescriber that an on-demand dose is necessary and risks of therapy continue to outweigh the benefits?	<b>Yes:</b> Approve based on standard FDA dosing for treatment of a single acute attack (see <b>Table 1</b> ).  Document attack severity if available	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
5. Since initiation of therapy, has the number or severity of hereditary angioedema attacks decreased?	<b>Yes:</b> Go to #6  Document change in attack frequency or severity	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
6. Has the patient been attack free for at least 6 months?	<b>Yes:</b> Go to #7	<b>No:</b> Approve for up to 12 months.
7. Is there documentation from the prescriber that they have evaluated continued necessity of long-term prophylactic treatment at the current dose?	<b>Yes:</b> Approve for up to 6 months.	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

Notes on adverse effects of treatment:

Bertralstat

- Doses above 150 mg daily have been associated with QT prolongation. Dose adjustment is recommended for patients with moderate to severe hepatic impairment or with concomitant p-glycoprotein or BCRP inhibitors. Avoid use with p-glycoprotein inducers.

C1 esterase inhibitors

- In clinical trials of patients with moderate to severe hereditary angioedema attacks, use of C1 esterase inhibitors improved the duration of symptoms by an average 1-2 hours compared to placebo. Prophylactic use has only been evaluated in patients with more than 2 attacks per month.
- Hypersensitivity reactions have been observed with C1 esterase inhibitors. Due to the risk of anaphylaxis, it is recommended that all patients prescribed human derived C1 esterase inhibitors have epinephrine immediately available.
- Serious arterial and venous thrombotic events have been reported with use of C1 esterase inhibitors, particularly in patients with pre-existing risk factors for thromboembolism. The exact incidence of thrombosis with C1 esterase inhibitors is unclear. In patients using prophylactic therapy with Cinryze®, over an average of 2.6 years, 3% of patients experienced thrombosis.

Ecallantide

- The average improvement in symptoms compared to placebo at 4 hours after treatment of an acute attack was 0.4 points on a 0-3 point scale.
- Ecallantide has a box warning for anaphylaxis. In clinical trials, 3-4% of patients treated with ecallantide experienced anaphylaxis. Risks of treatment should be weighed against the benefits.

Icatibant

- In clinical trials of icatibant for acute attacks, time to 50% overall symptom improvement was 17.8 hours better than placebo (19 vs. 2 hours). A second study demonstrated no difference from placebo in time to symptom

improvement. There are no data available on quality of life, daily activities, physical or mental functioning with use of icatibant.

#### Lanadelumab-flyo

- Prophylactic use has only been evaluated in patients with more than 1 moderate-severe attack per month. Hypersensitivity reactions were observed in 1% of patients treated with C1 esterase inhibitors. Elevated liver enzymes were also observed more frequently with lanadelumab compared to placebo (2% vs. 0%), and the long-term safety is unknown.

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*Implementation: 7/1/2021; 5/1/19*