Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM005.0226	**HEMATOLOGICAL AGENTS** **PROPHYLACTIC HEREDITARY ANGIOEDEMA THERAPY** See Appendix 2 for medications covered by policy
Effective Date: 4/1/2026	**Review/Revised Date**: 06/10, 06/11, 12/11, 04/12, 10/12, 12/12, 10/13, 10/14, 10/15, 10/16, 10/17, 09/18, 11/18, 10/19, 10/20, 01/21, 10/21, 03/22, 11/22, 11/22, 10/24, 10/25, 12/25 (snm)
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Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For **initiation of therapy** for prophylaxis of hereditary angioedema (HAE) attacks, all the following criteria (1-4) must be met:

1. Diagnosis of HAE confirmed by a history of recurrent angioedema and one of the following (a or b):
    a. For HAE Type I and Type II, documentation of one of the following (per laboratory standard):
        i. Type 1 HAE: Decreased quantities of C4 level, C1-INH protein (antigenic) level, and C1-INH function level OR
        ii. Type 2 HAE: Decreased quantities of C4 level and C1-INH function level (C1-INH protein (antigenic) level may be normal or elevated)
    b. For HAE with normal C1-INH:
        i. Normal or near normal C4, C1-INH antigen, and C1-INH function, and at least one of the following:
            1) Presence of a mutation in the C1-INH gene altering protein synthesis and/or function
            2) Positive family history for HAE and attacks lack response to high dose antihistamines or corticosteroids

2. Documentation of at least two HAE attacks per month on average for the past three months despite removal of triggers (such as estrogen containing oral contraceptives, angiotensin converting enzyme inhibitors) unless medically necessary
3. Dose and frequency are in accordance with the Food and Drug Administration-approved labeling
4. For coverage of **Cinryze:** Documentation of trial and failure, intolerance, or contraindication to Haegarda

For Patients Established on Therapy, all the following criteria (1-3) must be met**:**
1. Patient has had a of positive response to therapy (such as a reduction of frequency and/or severity of HAE attacks)
2. Dose and frequency are in accordance with the Food and Drug Administration-approved labeling
3. For **Takhzyro**: For patients established on Takhzyro that are well-controlled (such as attack free) for more than six months, the approved dose will be 300 mg every four weeks

EXCLUSION CRITERIA:
Concurrent use with other products indicated for prophylaxis to prevent attacks of hereditary angioedema

AGE RESTRICTIONS:
Age appropriate per FDA label

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, an immunologist or an allergist

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year

QUANTITY LIMITS:
Andembry: 1.2 mL per 28-day supply
Dawnzera: 0.8 mL per 28-day supply
Takhzyro: Two vials or syringes per 28-day supply
Orladeyo: 30 capsules (150 mg each) per 30-day supply

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

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Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Hereditary angioedema is a rare, genetic, and potentially life-threatening disorder associated with recurrent attacks of severe swelling in various parts of the body, including the throat. Medications for hereditary angioedema (HAE) can be categorized into on-demand therapies taken during an acute attack and therapies for prophylaxis of attacks. International guidelines and consensus documents recommend that all attacks be considered for treatment and that long-term prophylaxis be considered in all patients for whom on-demand therapy is insufficient to minimize effects of the disease.

FDA APPROVED INDICATIONS:

Andembry is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients aged 12 years and older.

Cinryze is indicated for routine prophylaxis against angioedema attacks in adults, adolescents and pediatric patients (six years old and above) with hereditary angioedema (HAE).

Dawnzera is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 12 years of age and older.

Haegarda is indicated for routine prophylaxis to prevent hereditary angioedema (HAE) attacks in patients six years of age and older.

Takhzyro is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients two years and older.

Orladeyo is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients two years and older.

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POSITION STATEMENT:

- HAE is a condition characterized by acute attacks of sudden edema formation in the skin or in the walls of the upper respiratory tract or gastrointestinal tract. HAE can be characterized into several subtypes:
    - Type I and II (also called HAE-C1INH) are characterized by C1INH deficiencies/dysfunction and is associated with abnormal C1INH and complement protein levels[6]
    - HAE with normal C1INH (HAE-nC1INH), previously known as Type III, is characterized by normal C1INH and complement studies but may be associated with mutations in the C1-INH gene altering protein synthesis and/or function[7]
- Diagnosis[6,7]
    - HAE-C1INH
        - A history of recurrent angioedema in the absence of concomitant urticaria and no concomitant use of medication known to cause angioedema
        - Low (50% of normal) C1INH antigenic or functional level
        - Low C4 level (either at baseline or during an attack
    - HAE-nC1INH
        - A history of recurrent angioedema in the absence of concomitant urticaria and no concomitant use of medication known to cause angioedema
        - Documented normal or near normal C4, C1-INH antigen, and C1-INH function
        - Either (1) Demonstration of a mutation associated with the disease OR (2) A positive family history of recurrent angioedema and documented lack of efficacy of high-dose antihistamine therapy (i.e., cetirizine at 40 mg/d or the equivalent) for at least 1 month or an interval expected to be associated with 3 or more attacks of angioedema, whichever is longer
        - Identified genes associated with mutations in HAE-nC1INH include: *FXII, ANGPT1, PLG, KNG1, MYOF, HS3OST6*
- Cinryze and Haegarda are made from human blood and may carry the risk of transmission of infectious agents (e.g., viruses, and theoretically, the Creutzfeldt-Jakob (CJD) agent). Serious arterial and venous thromboembolic events have also been reported with IV formulation.
- Takhzyro is the first human monoclonal antibody that targets plasma kallikrein to prevent attacks of edema. It differs from Cinryze and Haegarda, which are both proteins designed to replace the missing C1 esterase inhibitor in HAE patients. Per the package insert, the recommended starting dose is 300 mg

every two weeks. A dosing interval of 300 mg every four weeks is also effective and may be considered if the patient is well-controlled (e.g., attack free) for more than six months.
    - Commonly reported adverse reactions were headache, nausea, rash and vomiting, and injection site reactions.
- Orladeyo is the first oral prophylaxis agent that inhibits plasma kallikrein to prevent attacks of edema.
- Andembry is the first monoclonal antibody therapy to specifically target activated factor XII (FXIIa).

BILLING GUIDELINES AND CODING:

CODES*		
HCPCS	J0598	Injection, c-1 esterase inhibitor (human), cinryze, 10 units
	J0599	Injection, c-1 esterase inhibitor (human), haegarda, 10 units
	J0593	Injection, lanadelumab-flyo,1 mg
	J3590	Injection, garadacimab, unclassified biologic
	J3490	Injection, donidalorsen, unclassified drug
CPT	96372	Ther/proph/diag inj sc/im
	96374	Ther/proph/diag inj iv push
	96401	Chemo anti-neopl sq/im
N/A	N/A	Orladeyo capsule [Pharmacy benefit]

*Coding Notes:
• The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
• HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as “medically unlikely edits” (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCE/RESOURCES:

1. Relevant package inserts.
2. Zuraw BL, Bernstein JA, Lang DM et al. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol.* 2013;131(6):1491.
3. Lang DM, Aberer W, Bernstein JA et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol*. 2012;109(6):395

4. Magerl M, Germenis AE, Mass C et al. Hereditary Angioedema with Normal C1 Inhibitor. *Immunol Allergy Clin N Am*. 2017;37(3)571-584
5. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update. *European Journal of Allergy and Clinical Immunology*. 2022; 77(7): 1961-1990.
6. Busse PJ, Christiansen, SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2021;9(1):132-150.e3.
7. Zuraw, B.L., Bork, K., Bouillet, L. *et al.* Hereditary Angioedema with Normal C1 Inhibitor: an Updated International Consensus Paper on Diagnosis, Pathophysiology, and Treatment. *Clinic Rev Allerg Immunol* 68, 24 (2025).

APPENDIX 1: Complement Studies[2]

HAE Type	C4 (10-40mg/dL)*	C1INH Protein (21-39mg/dL)	C1 Function (greater or equal to 68%)**	C1q (5.0-8.6mg/dL)
Type I	Low	Low	Low	Normal
Type II	Low	Normal or Elevated	Low	Normal
HAE-nC1 (Type III)	Normal	Normal	Normal	Normal

*The normal range for C4 is extremely wide and may be reported as a concentration, absolute level, or percentage of normal. If the C4 level is presented in mg without a percent, 25 mg would be considered a normal level (100 percent), and levels less than 10 mg are strongly suggestive of C1INH deficiency (pathologic), while levels between 10 and 15 mg are possibly pathologic, and levels greater than 15 mg are not pathologic.
** 41-67% value is equivocal; less than or equal to 40% is abnormal

APPENDIX 2: Medication Availability

Drug	Use	Formulation	Availability	Dose
Andembry (garadacimab)	Prophylaxis	SQ	200mg/1.2mL prefilled syringe and autoinjector	400 mg (two injections of 200 mg) first day of treatment followed by 200 mg every month
Cinryze (C1 Esterase Inhibitor)	Prophylaxis	IV	500 units/vial	**Age 12 and older** 1000 units every 3-4 days; up to 2000 units every 3-4 days **Age 6 to 11:** 500 units every 3-4 days
Dawnzera (donidalorsen)	Prophylaxis	SQ	80 mg/0.8 mL autoinjector	80 mg every 8 weeks
Haegarda (C1 Esterase Inhibitor)	Prophylaxis	SQ	2000 units/vial 3000 units/vial	60 units/kg every 3-4 days
Orladeyo (berotralstat)	Prophylaxis	PO	Capsule: 110 mg, 150 mg	One capsule daily
Takhzyro (lanadelumab)	Prophylaxis	SQ	300 mg/2 ml vial 300 mg/2 ml syringe 150 mg/ml syringe	**Adults** 300 mg every two weeks. Dosing every four weeks may be considered in some patients **Peds** Age 2 to 6: 150mg every four weeks Age 6 to 12: 150mg every two weeks