# Drug Coverage Policy

**Effective Date.....11/15/2026**
**Coverage Policy Number.....IP0334**
**Policy Title.....Takhzyro**

# Hereditary Angioedema – Takhzyro

- Takhzyro® (lanadelumab-flyo subcutaneous injection – Shire/Takeda)

***INSTRUCTIONS FOR USE***
*The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.*

**OVERVIEW**
Takhzyro, a human monoclonal antibody inhibitor of plasma kallikrein, is indicated for **prophylaxis to prevent attacks of hereditary angioedema (HAE)** in patients ≥ 2 years of age.[1]

**Guidelines**
According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1 esterase inhibitor (C1-INH) antigenic level, and C1-INH functional level.[2] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The decision on when to use long-term prophylaxis cannot be made on rigid criteria but should reflect the needs of the individual patient. First-line medications for HAE I/II include intravenous C1-INH, Haegarda® (C1-INH [human] subcutaneous injection), or Takhzyro. The guideline was written prior to approval of Orladeyo® (berotralstat capsules).

According to World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2025), it is recommended to evaluate for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration.[3] The following therapies are supported as first-line options for long-term prophylaxis: subcutaneous plasma-derived C1-INH (Haegarda), Takhzyro, Orladeyo, Dawnzera™ (donidalorsen subcutaneous injection), and Andembry® (garadacimab subcutaneous injection). With regard to plasma-derived C1-INH, it is noted that Haegarda provides a more consistent plasma C1-INH concentrations than the intravenous route and reduces venous access-related complications, such as thrombosis risk. Of note, androgens are not recommended in the first-line setting for long-term prophylaxis.

A Phase III trial comparing Takhzyro with placebo for prophylactic use in HAE with normal C1-INH failed to demonstrate a statistically significant difference in reducing the number of attacks.[4]

## Coverage Policy

**POLICY STATEMENT**
Prior Authorization is required for benefit coverage of Takhzyro. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Takhzyro as well as the monitoring required for adverse events and long-term efficacy, approval requires Takhzyro to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met initial therapy criteria for Takhzyro for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., currently receiving Takhzyro). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Takhzyro, initial therapy criteria must be met.

**Documentation:** Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, medical test results, and prescription claims records. All documentation must include patient-specific identifying information.

**Takhzyro is considered medically necessary when the following are met:**

**FDA-Approved Indication**

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency - Prophylaxis.** Approve Takhzyro for 1 year if the patient meets ONE of the following (A or B):
   **A.** Initial therapy. Approve if the patient meets BOTH of the following (i and ii):

**i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
**a.** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
**b.** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND

**ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

**B.** Patient is currently receiving Takhzyro prophylaxis. Approve if the patient meets ALL of the following (i, ii, and iii):
Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Takhzyro for this indication through the Coverage Review Department, review under criteria for Initial Therapy.

**i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

**ii.** According to the prescriber, the patient has had a favorable clinical response since initiating Takhzyro prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND
Note: Examples of a favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.

**iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

**Dosing**. Approve ONE of the following dosing regimens (A, B, or C):

**A.** For patients who are ≥ 12 years of age: Approve a dose of 300 mg per injection, administered subcutaneously no more frequently than once every 2 weeks; OR

**B.** For patients who are 6 to < 12 years of age: Approve a dose of 150 mg per injection, administered subcutaneously no more frequently than once every 2 weeks; OR

**C.** For patients who are < 6 years of age: Approve a dose up to 150 mg per injection, administered subcutaneously no more frequently than once every 4 weeks

**Conditions Not Covered**

**Takhzyro for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):**

1. **Concomitant Use with Other Hereditary Angioedema (HAE) Prophylactic Therapies.**
Takhzyro has not been studied in combination with other prophylactic therapies for HAE, and combination therapy for long-term prophylactic use is not recommended. Patients may use other medications, including Cinryze (C1 esterase inhibitor [human] intravenous infusion), for on-demand treatment of acute HAE attacks, and for short-term (procedural) prophylaxis.
Note: Examples of other HAE prophylactic therapies include Cinryze (C1 esterase inhibitor [human] intravenous infusion), Haegarda (C1 esterase inhibitor [human] subcutaneous injection), and Orladeyo (berotralstat capsules).

## Coding Information

**Note:** 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

| HCPCS Codes | Description |
|---|---|
| J0593 | Injection, lanadelumab-flyo, 1 mg (Code may be used for Medicare when drug administered under direct supervision of a physician, not for use when drug is self-administered) |

## References


1. Takhzyro® subcutaneous injection [prescribing information]. Lexington, MA: Takeda; August 2026.
2. 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.
3. Vazquez DO, Giavina-Bianchi P, Josviack D, et al. The 2025 WAO guidelines for the classification, diagnosis, and treatment of hereditary angioedema, with consideration of worldwide disparities. *World Allergy Organ J*. 2026; 19.
4. Riedl MA, Staubach P, Farkas H, et al. Lanadelumab for prevention of attacks of non-histaminergic normal C1 inhibitor angioedema: results from the randomized, double-blind CASPIAN study and CASPIAN open-label extension. *Front. Immunol*. 2025 May 21;16:1502325.


## Revision Details

| Summary of Changes | Review Date | Effective Date |
|---|---|---|
| No criteria changes | 10/31/2024 | 1/1/2025 |
| **Policy Title.**<br>**Updated** from "Hereditary Angioedema - Lanadelumab-flyo" **to** "Hereditary Angioedema - Takhzyro"<br><br>**Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency - Prophylaxis**<br>**Added** "Due to C1 Inhibitor (C1-INH) Deficiency" to indication name<br>**Added** "Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b): Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement."<br>**Removed** "Confirmed pathogenic variant in the *SERPING1, F12, ANGPT1*, *PLG* or *KNG1* gene" | 11/20/2025 | 1/1/2026 |

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|---|---|---|
| **Removed** "Has low C1-INH antigenic levels (less than 50% of normal) at baseline, as documented by laboratory reference values"<br>**Removed** "Takhzyro will not be concomitantly administered with other FDA-approved prophylactic treatments for HAE (for example, Cinryze®, Haegarda®, or Orladeyo®)"<br>**Added** "a physician who specializes in the treatment of HAE or related disorders" to specialist requirement.<br>**Added** criteria for Patient is currently receiving Takhzyro prophylaxis<br><br>**Conditions Not Covered**<br>**Removed** C1-Inhibitor normal (levels and function) episodes of angioedema not related to a documented pathogenic variant in the F12, ANGPT1, PLG, or KNG1 gene. | | |
| No criteria changes | 11/5/2026 | 11/15/2026 |

The policy effective date is in force until updated or retired.

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