# Clinical Policy: Lanadelumab-fylo (Takhzyro)

Reference Number: CP.PHAR.396
Effective Date: 12.01.18
Last Review Date: 12.23
Line of Business: Commercial*, Medicaid

Coding Implications
Revision Log

**See Important Reminder at the end of this policy for important regulatory and legal information.**

## Description

Lanadelumab-fylo (Takhzyro™) is a human monoclonal antibody that inhibits the proteolytic activity of kallikrein to reduce the generation of bradykinin.

**These criteria do NOT apply to California Commercial Exchange Plans. Requests for California Commercial Exchange Plans should be reviewed using HIM.PA.172.*

## FDA Approved Indication(s)

Takhzyro is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 2 years and older.

## Policy/Criteria

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

It is the policy of health plans affiliated with Centene Corporation® that Takhzyro is **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Hereditary Angioedema*** (must meet all)**:**

**These criteria do NOT apply to California Commercial Exchange Plans. Requests for California Commercial Exchange Plans should be reviewed using HIM.PA.172.*

1. Diagnosis of HAE confirmed by a history of recurrent angioedema and one of the following (a or b):
   a. Low C4 level and low C1-INH antigenic or functional level (*see Appendix D)*;
   b. Normal C4 level and normal C1-INH level, and at least one of the following (i or ii):
      i. Presence of a mutation associated with the disease (*see Appendix D*);
      ii. Family history of angioedema, and documented failure of high-dose antihistamine therapy (i.e., cetirizine 40 mg/day or equivalent) for at least 1 month or an interval expected to be associated with 3 or more attacks of angioedema, whichever is longer;
2. Prescribed by or in consultation with an allergist, hematologist, or immunologist;
3. Age ≥ 2 years;
4. Prescribed for long-term prophylaxis of HAE attacks and request meets one of the following (a, b, or c):
   a. Member experiences more than one severe event per month;
   b. Member is disabled more than five days per month;

c. Member has history of previous airway compromise;
5. For members age ≥ 6 years: Failure of Haegarda®, unless contraindicated or clinically significant adverse effects are experienced;
6. Member is not using Takhzyro in combination with another FDA-approved product for long-term prophylaxis of HAE attacks (e.g., Cinryze®, Haegarda®, Orladeyo™);
7. Dose does not exceed one of the following (a, b, or c):
   a. For adult and pediatric members ≥ 12 years of age, both (i and ii):
      i. 300 mg every 2 weeks;
      ii. 1 vial or 1 syringe every 2 weeks;
   b. For pediatric members 6 to < 12 years of age, both (i and ii):
      i. 150 mg every 2 weeks;
      ii. 1 syringe every 2 weeks;
   c. For pediatric members 2 to < 6 years of age, both (i and ii):
      i. 150 mg every 4 weeks;
      ii. 1 syringe every 4 weeks.

**Approval duration:**
**Medicaid**– 6 months
**Commercial –** 6 months or to the member's renewal date, whichever is longer

**B. Other diagnoses/indications** (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial and CP.PMN.53 for Medicaid.

## II. Continued Therapy

**A. Hereditary Angioedema** (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy as evidenced by reduction in attacks from baseline;
3. Member is not using Takhzyro in combination with another FDA-approved product for long-term prophylaxis of HAE attacks (e.g., Cinryze, Haegarda, Orladeyo);

4. For age 6 years to < 12 years: Request is for 150 mg every 4 weeks, unless documentation supports member is not well-controlled (e.g., attack(s) within the last 6 months);
5. For age ≥ 12 years: Request is for 300 mg every 4 weeks, unless documentation supports member is not well-controlled (e.g., attack(s) within the last 6 months);
6. If request is for a dose increase, new dose does not exceed one of the following (a, b, or c):
   a. For adult and pediatric members ≥ 12 years of age, both (i and ii):
      i. 300 mg every 2 weeks;
      ii. 1 vial or 1 syringe every 2 weeks;
   b. For pediatric members 6 to < 12 years of age, both (i and ii):
      i. 150 mg every 2 weeks;
      ii. 1 syringe every 2 weeks;
   c. For pediatric members 2 to < 6 years of age, both (i and ii):
      i. 150 mg every 4 weeks;
      ii. 1 syringe every 4 weeks.

**Approval duration:**
**Medicaid** – 12 months
**Commercial –** 6 months or to the member's renewal date, whichever is longer

**B. Other diagnoses/indications** (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial and CP.PMN.53 for Medicaid.

## III. Diagnoses/Indications for which coverage is NOT authorized:

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial and CP.PMN.53 for Medicaid or evidence of coverage documents.

## IV. Appendices/General Information

*Appendix A: Abbreviation/Acronym Key*

CI-INH: C1 esterase inhibitor
C4: complement component 4
FDA: Food and Drug Administration
HAE: hereditary angioedema
HAE-nl-C1INH: hereditary angioedema with normal C1 inhibitor

*Appendix B: Therapeutic Alternatives*
*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| cetirizine | 40 mg/day (*off-label*)<br>Typical dosing range (mg/day): 10 mg/day<br>*US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema* | 40 mg/day (*off-label*) |
| C1 esterase inhibitor (Haegarda®) | 60 IU/kg body weight SC twice weekly (every 3 or 4 days) | Based on weight, 60 IU/kg/dose |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*
None reported

*Appendix D: General Information*
- Diagnosis of HAE:
  - There are two classifications of HAE: HAE with C1-INH deficiency (HAE-C1INH, further broken down into Type 1 and Type II) and HAE with normal C1-INH (also known as HAE-nl-C1INH). HAE-nl-C1INH was previously referred to as type III HAE, but this term is obsolete and should not be used.
  - In both Type I (~85% of cases) and Type II (~15% of cases), C4 levels are low. C1-INH antigenic levels are low in Type I while C1-INH functional levels are low in Type II. Diagnosis of Type I and II can be confirmed with laboratory tests. Reference ranges for C4 and C1-INH levels can vary across laboratories (see below for examples); low values confirming diagnosis are those which are below the lower end of normal.

| Laboratory Test & Reference Range | Mayo Clinic | Quest Diagnostics | Lab Corp |
|---|---|---|---|
| C4 | 14 – 40 mg/dL | 13-57 mg/dL (age- and gender-specific ranges) | 10-38 mg/dL (age- and gender-specific ranges) |
| C1-INH, antigenic | 19 – 37 mg/dL | 21 – 39 mg/dL | 21 – 39 mg/dL |
| C1-INH, functional | Normal: > 67%<br>Equivocal: 41 – 67%<br>Abnormal: < 41% | Normal: ≥ 68%<br>Equivocal: 41 – 67%<br>Abnormal: ≤ 40% | Normal: > 67%<br>Equivocal: 41 – 67%<br>Abnormal: < 41% |

- HAE-nl-C1INH, on the other hand, presents with normal C4 and C1-INH levels. Some patients have a known associated mutation, while others have no identified genetic indicators. HAE-nl-C1INH is very rare, and there are no laboratory tests to confirm the diagnosis; mutations in 6 genes causing HAE-nl-C1INH have been identified:

| Identified Genes Associated with Mutations in HAE-nl-C1INH |
|---|
| *F12* |
| *ANGPT1* |
| *PLG* |
| *KNG1* |
| *MYOF* |
| *HS3ST6* |

## V. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| HAE attack prophylaxis | Adult and pediatric patients ≥ 12 years of age<br>300 mg SC every 2 weeks<br>A dosing interval of 300 mg every 4 weeks may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months<br><br>Pediatric patients 6 to < 12 years of age<br>150 mg SC every 2 weeks<br>A dosing interval of 150 mg every 4 weeks may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months<br><br>Pediatric patients 2 to < 6 years of age<br>150 mg SC every 4 weeks | See dosing regimen |

## VI. Product Availability

- Single-dose vial: 300 mg/2 mL (150 mg/mL) solution
- Single-dose prefilled syringes: 300 mg/2 mL (150 mg/mL) solution, 150 mg/1 mL solution

## VII. References

1. Takhzyro Prescribing Information. Lexington, MA: Shire ViroPharma Incorporated; February 2023. Available at: https://www.takhzyro.com. Accessed April 21, 2023.
2. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy. 2022;77(7):1961-1990.
3. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy.* 2014; 69(5): 602-616.

4. Zuraw B, Bernstein J, Lang D. 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.
5. Busse PJ, Christiansen SC, Reidl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol*. 2021; 9(1): 132-150.e3.
6. Mayo Clinic Laboratories [internet database]. Rochester, Minnesota: Mayo Foundation for Medical Education and Research. Updated periodically. Accessed May 17, 2023.
7. Quest Diagnostics ® [internet database]. Updated periodically. Accessed May 17, 2023.
8. LabCorp [internet database]. Burlington, North Carolina: Laboratory Corporation of America. Updated periodically. Accessed May 17, 2023.

**Coding Implications**

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

| HCPCS Codes | Description |
|---|---|
| J0593 | Injection, lanadelumab-flyo, 1 mg |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 1Q 2020 annual review: HAE lab reference range updated; removed rheumatologist specialty for alignment; revised dosing criteria for dose reduction if member is well-controlled per PI; added coding implications; references reviewed and updated. | 11.04.19 | 02.20 |
| 1Q 2021 annual review: no significant changes; references reviewed and updated. | 10.08.20 | 02.21 |
| Per June SDC and prior clinical guidance, added redirection to Haegarda. | 06.02.21 | 08.21 |
| 1Q 2022 annual review: updated diagnosis criteria to include a recurrent history of angioedema and either an associated mutation or family history of angioedema with failure of high-dose antihistamines for HAE-nl-C1INH; references reviewed and updated. | 11.08.21 | 02.22 |
| RT4: New dose formulation of prefilled syringe added to policy. | 03.01.22 | |
| Template changes applied to other diagnoses/indications and continued therapy section. | 09.23.22 | |
| 1Q 2023 annual review: no significant changes; added note that Takhzyro prefilled syringe request for HIM line of business pharmacy benefit is non-formulary and added reference to the formulary exception policy HIM.PA.103; updated Appendix D lab reference range and mutations associated with HAE; references reviewed and updated. | 11.03.22 | 02.23 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| RT4: updated FDA approved indication with the pediatric extension and added new lower-volume syringe; added maximum quantity criteria to align with FDA-labeled maximum dosing; clarified that Haegarda failure requirement applied to members age ≥ 6 years per Haegarda FDA-labeled indication; removed pharmacy benefit disclaimer language for HIM Takhzyro prefilled syringe requests per HIM formulary status. | 02.22.23 | |
| 3Q 2023 annual review: no significant changes; references reviewed and updated. | 04.21.23 | 08.23 |
| Per August SDC, removed HIM line of business. | 08.22.23 | 12.23 |
| Per SDC, added the following clarification under the description and initial approval criteria sections: "These criteria do NOT apply to California Commercial Exchange Plans. Requests for California Commercial Exchange Plans should be reviewed using HIM.PA.172" | 02.15.24 | |

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

**Note:**
**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.