PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – Takhzyro Prior Authorization Policy
- Takhzyro® (lanadelumab-flyo subcutaneous injection – Shire/Takeda)

REVIEW DATE: 10/09/2024

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 AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. 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.

CIGNA NATIONAL FORMULARY COVERAGE:

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 (2021), 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: plasma-derived C1-INH (87% agreement), Takhzyro (89% agreement), and Orladeyo (81% agreement). With regard to plasma-derived C1-INH, it is noted that Haegarda provided very good and dose-dependent preventative effects on the occurrence of HAE attacks; the subcutaneous route may provide more convenient administration and maintain improved steady-state plasma concentrations compared with the intravenous route. Of note, androgens are not recommended in the first-line setting for long-term prophylaxis. Recommendations are not made regarding long-term prophylaxis in HAE with normal C1-INH.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Takhzyro. 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, and prescription claims records.

- **Takhzyro® (lanadelumab-flyo subcutaneous injection – Shire/Takeda) is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):**

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.

CONDITIONS NOT COVERED

- **Takhzyro® (lanadelumab-flyo subcutaneous injection – Shire/Takeda) is(are) considered experimental, investigational or unproven for ANY other use(s) 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).

REFERENCES

1. Takhzyro® subcutaneous injection [prescribing information]. Lexington, MA: Takeda; February 2023.
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. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	It was added to the Policy Statement that a person who has previously met initial therapy criteria for Takhzyro for the requested indication under the Coverage Review Department and is currently receiving Takhzyro, is only required to meet continuation of therapy criteria (i.e., patient is currently receiving Takhzyro). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Takhzyro, initial criteria must be met. In addition, the following changes were made: **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient is currently receiving Takhzyro prophylaxis", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through another entity. Also added the word "type" before II while referring to diagnosis of HAE types.	09/20/2023
Annual Revision	No criteria changes.	10/09/2024