lanadelumab-flyo (Takhzyro™)

Policy # 00654
Original Effective Date: 12/19/2018
Current Effective Date: 01/08/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of lanadelumab-flyo (Takhzyro™)‡ for routine prophylaxis against hereditary angioedema (HAE) attacks to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility will be considered for the use of lanadelumab-flyo (Takhzyro) for routine prophylaxis against HAE attacks when the following criteria are met:

- Patient has a diagnosis of HAE confirmed by appropriate laboratory test(s); AND
- Patient has a history of laryngeal edema or airway compromise with an episode of HAE OR a history of at least 2 HAE attacks per month.
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of lanadelumab-flyo (Takhzyro) in the absence of a history of laryngeal edema or airway compromise with an episode of HAE OR in the absence of a history of at least 2 HAE attacks per month to be to be **not medically necessary.****

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of lanadelumab-flyo (Takhzyro) for a patient without a confirmed diagnosis of HAE or for any indication other than routine prophylaxis of HAE to be **investigational.***

Background/Overview

Takhzyro is a monoclonal antibody indicated for prophylaxis of attacks of hereditary angioedema (HAE). It inhibits plasma kallikrein to prevent the production of bradykinin, a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with HAE. Takhzyro is dosed at 300 mg subcutaneously once every 2 weeks and may be self-administered after proper training by a healthcare professional. A dose of 300 mg every 4 weeks may be considered if the patient is attack-free for more than 6 months.

HAE is a relatively rare (1:10,000 to 1:50,000 prevalence) autosomal dominant genetic disease estimated to impact about 6,000 individuals in the US. It is a potentially life-threatening disease in which there is a deficiency of or lack of functionally active complement-1 esterase inhibitor (C1-INH) in the blood. HAE is characterized by recurrent episodes of sudden attacks of non-pruritic, non-pitting, localized edema. The swelling can occur almost anywhere, but is commonly found in the following body parts: extremities, intestines (abdomen), face, larynx, and genitals. Swelling attacks can occur unpredictably and vary in severity and frequency. HAE is inherited in an autosomal dominant manner, and family history is a strong predictor of the disease. However, spontaneous mutation accounts for up to 25% of newly diagnosed cases.

There are three types of HAE. Type I HAE accounts for 80-85% of all cases and results in both decreased antigenic and functional levels of C1-INH. Type II HAE accounts for about 15% of all cases and results in normal antigenic C1-INH levels but decreased functional C1-INH levels. The third variant of HAE is known as HAE with normal C1-INH (previously referred to as HAE type III or estrogen-dependent HAE) and is found predominantly in women.
It has been suggested that HAE with normal C1-INH is caused by activating mutations in the gene for coagulation factor XII. HAE is diagnosed by clinical history, diagnostic tests, and exclusion of other

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causes of angioedema. The specific tests required to make the diagnosis include C4, C1q, and C1-INH (antigenic and functional level). Genetic testing is not necessary to confirm the diagnosis of HAE.

Symptoms of HAE can present at any age, but there appears to be an increased occurrence of HAE after puberty and a reduction after menopause, suggesting a hormone-influenced mechanism. Attacks are commonly triggered by stress, hormonal changes, medical procedures, trauma, or medications that impact bradykinin or hormone levels such as angiotensin-converting enzyme (ACE) inhibitors and estrogen-containing medications. In some cases, attacks occur without an apparent trigger. Attacks are usually preceded by a prodrome (usually a tingling sensation or painless, nonpruritic rash, skin tightness, and fatigue), which can occur 30 minutes to several hours before an HAE attack. As vascular permeability increases, swelling worsens gradually for the first 24 hours and subsides 48-72 hours after swelling reaches its peak. Unlike histamine-mediated allergic angioedema, HAE swelling attacks are not symmetrical and often extend locally. Edema may begin, worsen, and end in one anatomical location, or begin in one location and emerge in another location, or occur simultaneously in many locations. Abdominal attacks are thought to be the most debilitating attacks experienced by HAE patients. Severe attacks may cause obstruction of the gastrointestinal tract. Repeated attacks may lead to inadequate biliary/pancreatic drainage causing gallbladder disease or pancreatitis. Swelling involving the airway is less common but is potentially life-threatening. The time from symptom onset to asphyxiation ranges from 20 minutes to 14 hours. It has been reported that at least 50% of HAE patients will have a laryngeal attack at some point in their lives and many have these attacks repeatedly. Mortality rates are estimated at 15-30%, largely due to laryngeal edema.

Treatment of HAE is divided into prophylactic and on-demand treatment. Guidelines from the World Allergy Organization (2017) recommend that all HAE attacks be considered for on-demand treatment with either C1-INH, ecallantide (Kalbitor®)‡ or icatibant (Firazyr®)‡. The decision to begin long-term prophylaxis should be individualized and considered in all severely symptomatic patients with HAE type I or type II. At the time of guideline publication, approved treatments for long term prophylaxis included C1-INH and attenuated androgens.

Danazol is the only androgen that is FDA-approved for HAE prophylaxis and has traditionally been used prior to the availability of C1-INH. It is sometimes preferred due to oral administration and lower cost. However, the guidelines now recommend that androgens be used as second-line therapy due to the adverse event profile compared to currently available therapies. The guidelines have not been updated to include Takhzyro.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Takhzyro was approved in August 2018 for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years of age and older. In February 2023, the label was expanded to include pediatric patients aged 2-12 years of age.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Takhzyro for the prevention of angioedema attacks was demonstrated in a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The study included 125 adult and adolescent patients with Type I or II HAE who experienced at least one investigator-confirmed attack per 4 weeks during the run-in period. Patients were randomized into 1 of 4 parallel treatment arms, stratified by baseline attack rate, in a 3:2:2:2 ratio (placebo, lanadelumab 150 mg every 4 weeks, lanadelumab 300 mg every 4 weeks, lanadelumab 300 mg every 2 weeks) for the 26-week treatment period. Patients ≥18 years of age were required to discontinue other prophylactic HAE medications prior to entering the study; however, all patients were allowed to use rescue medications for treatment of breakthrough HAE attacks. The primary endpoint was the mean HAE attack rate throughout the treatment period. All treatment arms produced clinically meaningful and statistically significant reductions in the mean HAE attack rate compared to placebo.

The mean monthly attack rate in the placebo group was 1.97, it was 0.48 in the 150 mg every 4 week group, 0.53 in the 300 mg every 4 week group, and 0.26 in the 300 mg every 2 week group. This represented a 76-87% reduction in attacks relative to placebo.
Patients who completed Trial 1 were eligible to rollover into an open-label extension study. Rollover patients, regardless of randomization group in Trial 1, received a single dose of Takhzyro 300 mg at study entry and were followed until the first HAE attack occurred. All efficacy endpoints were exploratory in this uncontrolled, unblinded study. At week 4 post-dose, approximately 80% of patients who had been in the 300 mg every 2 weeks treatment group (n=25) in Trial 1 remained

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attack-free. After the first HAE attack, all patients received open-label treatment with Takhzyro 300 mg every 2 weeks.

References

1. Takhzyro [package insert]. Shire. Lexington, MA. Updated Feb 2023.
2. Takhzyro Drug Evaluation. Express Scripts. Updated Sept 2018.
3. Mauer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2017 revision and update. Allergy. 2018;73(8):1575-1596.

Policy History

Original Effective Date: 12/19/2018
Current Effective Date: 01/08/2024

12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. New policy.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/02/2021	Medical Policy Committee review
12/08/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2022	Medical Policy Committee review
12/14/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. Updated background information to reflect label update including pediatric patients aged 2 years and older.

Next Scheduled Review Date: 12/2024

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

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