berotralstat (Orladeyo™)

Policy # 00743
Original Effective Date: 04/12/2021
Current Effective Date: 04/10/2023

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 berotralstat (Orladeyo™)‡ for routine prophylaxis against hereditary angioedema (HAE) attacks in adolescents and adults to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility will be considered for the use of berotralstat (Orladeyo) for routine prophylaxis against HAE attacks in adolescents and adults when the following criteria are met:

- Patient has a diagnosis of Type I or II 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 berotralstat (Orladeyo) 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 **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 berotralstat (Orladeyo) for a patient without a confirmed diagnosis of HAE or for any indication other than routine prophylaxis of HAE to be **investigational.***

Background/Overview

Orladeyo is a plasma kallikrein inhibitor indicated for prophylaxis of attacks of hereditary angioedema (HAE). It binds to plasma kallikrein in order to prevent it from forming bradykinin, a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with HAE. Orladeyo is administered orally and is dosed as 150 mg once daily with food.

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. It should be noted that there are no randomized or controlled clinical trial data available with any therapy for use in HAE with normal C1-INH.

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HAE is diagnosed by clinical history, diagnostic tests, and exclusion of other causes of angioedema. The specific tests required to make the diagnosis include C4, C1a, and C1-INH (antigenic and functional level). Genetic testing is not necessary to confirm the diagnosis of HAE.

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 (e.g., danazol). Newer therapies include lanadelumab-flyo (Takhzyro™)‡ and Orladeyo.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Orladeyo was approved in December 2020 for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years of age and older.

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 Orladeyo for the prevention of angioedema attacks in patients 12 years of age and older with Type I or II HAE was demonstrated in Part 1 of a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The study included 120 adult and adolescent patients who experienced at least two investigator-confirmed attacks within the first 8 weeks of the run-in period and took at least one dose of study treatment. Patients were randomized into 1 of 3 parallel treatment arms, stratified by baseline attack rate, in a 1:1:1 ratio (Orladeyo 110 mg, Orladeyo 150 mg, or placebo once daily with food) for the 24-week treatment period. Patients discontinued other prophylactic HAE medications prior to entering the study; however, all patients were allowed to use rescue medications for treatment of breakthrough HAE attacks.

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A history of laryngeal angioedema attacks was reported in 74% of patients and 75% reported prior use of long-term prophylaxis. The median attack rate during the prospective run-in period (baseline attack rate) was 2.9 per month. Of the patients enrolled, 70% had a baseline attack rate of ≥2 attacks per month.

Orladeyo 150 mg and 110 mg produced statistically significant reductions in the rate of HAE attacks compared to placebo for the primary endpoint of percent rate reduction in HAE attack rate per 28 days. For the Orladeyo 150 mg group, the HAE attack rate was 1.31 versus a rate of 2.35 in the placebo group. This was statistically significant and represents a percent rate reduction of 44.2%.

References

1. Orladeyo [package insert]. BioCryst Pharmaceuticals, Inc. Durham, NC. Updated December 2020.
2. Orladeyo Prior Authorization Policy. Express Scripts. Updated December 2020.

Policy History

Original Effective Date: 04/12/2021
Current Effective Date: 04/10/2023
03/04/2021 Medical Policy Committee review
03/10/2021 Medical Policy Implementation Committee approval. New policy.
03/04/2021 Medical Policy Committee review
03/10/2021 Medical Policy Implementation Committee approval. Coverage criteria unchanged.
03/03/2022 Medical Policy Committee review
03/09/2022 Medical Policy Implementation Committee approval. Coverage criteria unchanged.
03/02/2023 Medical Policy Committee review
03/08/2023 Medical Policy Implementation Committee approval. Coverage criteria unchanged.
Next Scheduled Review Date: 03/2024

*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:

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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.