



sodium phenylbutyrate/taurursodiol (Relyvrio™)

Policy # 00831

Original Effective Date: 03/13/2023

Current Effective Date: 03/11/2024

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 sodium phenylbutyrate/taurursodiol (Relyvrio™)† for the treatment of amyotrophic lateral sclerosis (ALS) to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for sodium phenylbutyrate/taurursodiol (Relyvrio) will be considered when the following criteria are met:

- Initial
 - Patient has a definite or probable diagnosis of ALS based on the revised El Escorial criteria; AND
 - Patient is ≥18 years of age; AND
 - Onset of ALS symptoms began in the previous 18 months; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary** if not met.)*
 - Patient has a percent-predicted slow vital capacity (SVC) >60% based on gender, height, and age; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary** if not met.)*
 - Patient does not have a tracheostomy; AND

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*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary** if not met.)*

- Patient is on concurrent therapy with generic riluzole unless therapy with riluzole is contraindicated or previously not tolerated.

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

- Continuation

- Patient has an initial authorization for Relyvrio; AND
- Patient does not have a tracheostomy; AND

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary** if not met.)*

- According to prescriber, patient is benefitting from treatment with Relyvrio.

*(Note: This specific patient selection 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 sodium phenylbutyrate/taurursodiol (Relyvrio) when it has been greater than 18 months since the onset of symptoms, SVC is $\leq 60\%$, patient has a tracheostomy, or patient is not on concurrent therapy with riluzole to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of sodium phenylbutyrate/taurursodiol (Relyvrio) in patients who have a tracheostomy or who are not benefitting from treatment with Relyvrio 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 sodium phenylbutyrate/taurursodiol (Relyvrio) when patient selection criteria are not met (except those denoted to be **not medically necessary****) to be **investigational.***

Policy Guidelines

El Escorial Criteria

Diagnosis	El Escorial Revised Airlie House Criteria
Definite ALS	Upper motor neuron (clinical exam) and lower motor neuron (clinical, electrophysiological or neuropathological exam) signs: <ul style="list-style-type: none">Bulbar region and > 2 spinal regions ORThree spinal regions
Probable ALS	Upper and lower motor neuron signs in > 2 regions and upper signs rostral to lower signs
Probable ALS – laboratory-supported	<ul style="list-style-type: none">Upper and lower motor neuron signs in one region ORUpper signs alone in one region and lower signs via electrophysiological criteria of lower motor neuron loss > 2 regions
Possible ALS	<ul style="list-style-type: none">Upper and lower signs in one region ORUpper motor neuron signs alone in > 2 regions ORLower motor neuron signs rostral to upper motor neuron signs and unable to prove clinically probably ALS

Background/Overview

Relyvrio is a combination product of sodium phenylbutyrate and taurursodiol and is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults. Although the exact mechanism of action is unknown, it is thought that these agents alleviate stress on the endoplasmic reticulum and



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mitochondria of the body's cells. The recommended dose is one packet given orally or by a feeding tube once daily for 3 weeks. After 3 weeks, maintenance dosing increases to one packet twice daily.

ALS is a rapidly progressing, degenerative disease in which the patient's upper and lower motor neurons degenerate leading to loss of motor function. Patients with ALS present with painless, progressive muscle atrophy and weakness, which eventually leads to paralysis. Death due to respiratory failure typically occurs within 3-5 years of diagnosis. Approximately 14,000-15,000 people in the U.S. have ALS. The disease occurs most commonly in people aged 55-75 years. The El Escorial criteria were developed to standardize the diagnosis of ALS. Disease progression is monitored using the ALSFRS-R, a 13-question scale that assesses the patient's ability to perform normal daily activities such as speech, handwriting, cutting food, and climbing stairs. Each question is scored on a scale of 0-4 with higher scores representing greater functional ability.

Current treatment guidelines from the American Academy of Neurology (AAN) do not address Relyvrio or the other newer treatment option, Radicava®†. The parameter states that riluzole, the only other disease-modifying agent approved for ALS, is safe and effective for slowing disease progression to a modest degree and should be offered to patients with ALS. All other pharmacologic recommendations center on symptomatic management and palliative care.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Relyvrio was approved in September 2022 for the treatment of amyotrophic lateral sclerosis (ALS)

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 Relyvrio for the treatment of ALS was demonstrated in a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that evaluated Relyvrio in adult patients with ALS. For inclusion in the study, patients had to have a definite diagnosis of sporadic

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or familial ALS as defined by the revised El Escorial criteria, with symptom onset in the past 18 months, and a slow vital capacity (SVC) greater than 60% of predicted at screening. A total of 137 patients were randomized 2:1 to receive either Relyvrio (n=89) or placebo (n=48) for 24 weeks. Patients were administered the contents of one packet of Relyvrio or placebo, once daily for the first 3 weeks. After 3 weeks of treatment, the dose was increased to one packet twice daily if tolerated.

The prespecified primary efficacy endpoint was a comparison of the rate of reduction in the ALS Functional Rating Scale-Revised (ALSFRS-R) total scores from baseline to Week 24. The ALSFRS-R scale consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS. Each item is scored from 0-4, with higher scores representing greater functional ability. There was a statistically significant difference in the rate of reduction in the ALSFRS-R total score from baseline to Week 24 in Relyvrio patients compared to placebo-treated patients ($p=0.034$). The Relyvrio group had a LS Mean score of 29.06 and the placebo group had a LS mean total score of 26.73.

In a post hoc, long-term survival analysis, vital status was ascertained in 136 of 137 patients who were enrolled in Study 1. Longer median overall survival was observed in the patients originally randomized to Relyvrio compared to those originally randomized to placebo. This exploratory analysis should be interpreted cautiously given the limitations of data collected outside of a controlled study, which may be subject to confounding.

References

1. Relyvrio [package insert]. Amylyx Pharmaceuticals, Inc. Cambridge, MA. Updated September 2022.
2. Relyvrio Drug Evaluation. Express Scripts. Updated October 2022.

Policy History

Original Effective Date: 03/13/2023

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02/02/2023 Medical Policy Committee review

02/08/2023 Medical Policy Implementation Committee approval. New policy.

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02/01/2024 Medical Policy Committee review

02/14/2024 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 02/2025

***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.

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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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