09-J4000-42

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Reviewed: 04/10/24

Revised: 05/15/24

Subject: Sodium phenylbutyrate-taurursodiol (Relyvrio) for oral suspension

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Amyotrophic lateral sclerosis (ALS) is a debilitating disease caused by degeneration of cortical, brainstem, and spinal cord motor neurons and, in some cases, frontotemporal cortical neurons. The neurodegeneration results in progressive muscle weakness, muscle spasticity, dysarthria, dysphagia, cognitive and behavioral impairments, and other motor symptoms. The exact etiology of ALS is unclear but is likely due to multiple genetic (e.g., *C9orf72*, *TARDBP*, *SOD1*, *FUS* genes) and environmental factors. Onset typically occurs at age 50 to 75 years and is more frequently reported in males than females, with a lifetime risk of about 0.29% and 0.25%, respectively. Additionally, the annual incidence of ALS is about 2 to 3 cases for patients of European ancestry, 0.7 to 0.8 cases for patients of Asian ancestry, and 0.63 cases for patients of Native North American ancestry per 100,000 persons. Unfortunately, prognosis is poor with a median survival of 2 to 4 years, and respiratory insufficiency is the most common cause of death.

Patients presenting with suspected ALS are typically evaluated using the revised El Escorial/Arlie House criteria, which utilize clinical and electrophysiologic evaluations to ensure all the hallmark signs and symptoms are present while ruling out other neurodegenerative diseases. Once diagnosed, therapeutic options include riluzole (Rilutek tablets, Tiglutik suspension, and Exservan oral film) 50 mg orally twice daily, which modulates the actions of glutamate to slow disease progression, and edaravone (Radicava oral suspension), a free radical scavenger and antioxidant, as concomitant therapy or as monotherapy if the patient is intolerant to riluzole. On September 29, 2022, the FDA approved sodium phenylbutyrate-taurursodiol (Relyvrio) for the treatment of ALS.

The efficacy of sodium phenylbutyrate-taurursodiol (Relyvrio) was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial. A total of 137 patients were randomly assigned 2:1 to receive either sodium phenylbutyrate–taurursodiol (89 patients) at 3 g of sodium phenylbutyrate and 1 g of taurursodiol, administered once a day for 3 weeks and then twice a day, or placebo (48 patients). Inclusion criteria consisted of a definite ALS diagnosis per the revised El Escorial criteria, ALS symptom onset within the last 18 months, and a slow vital capacity (SVC) exceeding 60% of the predicted value. Patients with a tracheostomy or permanent assisted ventilation (> 22 hours per day) were not permitted to enroll. Concomitant use of riluzole and edaravone was permitted, with 77% of patients receiving riluzole or edaravone at or before trial entry and 28% receiving both. The primary endpoint was the rate of decline in

the total score for the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) from baseline to week 24 (possible total scores are zero to 48 with higher scores indicating better function; see Definitions). In the modified intention-to-treat population, 69% of the sodium phenylbutyrate–taurursodiol group and 77% of the placebo group completed the trial. The mean rate of change in the ALSFRS-R score was −1.24 points per month for sodium phenylbutyrate-taurursodiol and −1.66 points per month for placebo (difference, 0.42 points per month; 95% confidence interval, 0.03 to 0.81; P=0.03). Correction analyses for the use of riluzole and edaravone were conducted to validate the results and yielded similar rates of change. Secondary outcomes did not differ significantly between the two groups. Adverse events were similar between groups; however, sodium phenylbutyrate-taurursodiol was associated with more gastrointestinal symptoms (i.e., nausea, diarrhea, and abdominal pain) during the first 3 weeks. In general, sodium phenylbutyrate-taurursodiol appears to be an additional treatment option for patients with ALS.

On March 8, 2024, the manufacturer released the results of the PHOENIX trial, which was a phase III, randomized, double-blind, placebo-controlled, multicenter trial designed to further evaluated the safety and efficacy of sodium phenylbutyrate and taurursodiol (Relyvrio) as compared to placebo in patients with ALS. Enrolled patients included those 18 years of age and older with a diagnosis of definite or clinically probable ALS, a SVC of 55% or greater of the predicted value, and the time since the first symptom onset of less than 24 months. The study did not meet its prespecified primary endpoint, failing to reach statistical significance in the change from baseline in the ALSFRS-R total score at Week 48 (p=0.667). Additionally, the study did not reach statistical significance for its secondary endpoints (i.e., quality-of-life questionnaires, overall survival, and rate of decline in slow vital capacity). As a result of the PHOENIX trial, the manufacturer announced on April 4, 2024 that it will voluntarily discontinue the marketing of sodium phenylbutyrate and taurursodiol (Relyvrio) and will remove the product from the U.S. market. Sodium phenylbutyrate and taurursodiol (Relyvrio) is no longer available for new patients; however, patients currently on therapy who, in consultation with their provider, wish to continue can be transitioned to a free drug program available through the manufacturer.

POSITION STATEMENT:

Comparative Effectiveness

Sodium phenylbutyrate-taurursodiol (Relyvrio) **does not meet the definition of medical necessity** for all indications including, but not limited to, amyotrophic lateral sclerosis (ALS), as a clinical benefit has not been established.

Sodium phenylbutyrate-taurursodiol (Relyvrio) was granted FDA approval for the treatment of amyotrophic lateral sclerosis (ALS) in adults. This indication was approved based on a single, phase II clinical trial of 137 patients in the United States. The follow-up phase III trial failed to demonstrate a significance difference as compared to placebo in the change from baseline in the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) total score at Week 48, quality-of-life questionnaires, overall survival, and the rate of decline in slow vital capacity. The manufacturer is withdrawing the product from the U.S. market but will provide a free drug program for patients, in consultation with their provider, to continue their current therapy.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Sodium phenylbutyrate-taurursodiol (Relyvrio) is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults.
- The recommended dosage is 1 packet (3 g sodium phenylbutyrate and 1 g taurursodiol) administered orally or via feeding tube at 1 packet daily for the first 3 weeks followed by 1 packet twice daily thereafter.
- Administer sodium phenylbutyrate-taurursodiol (Relyvrio) before a snack or meal.
- To prepare the sodium phenylbutyrate-taurursodiol (Relyvrio) suspension empty one packet into a cup containing 8 ounces of room temperature water and stir vigorously prior to administration.
- The suspension must be taken within 1 hour of preparation.

Dose Adjustments

- The effect of renal or hepatic impairment on the pharmacokinetics of sodium phenylbutyrate-taurursodiol (Relyvrio) is unknown.

Drug Availability

- Sodium phenylbutyrate-taurursodiol (Relyvrio) for oral suspension is supplied in single-dose packets of white to yellow powder containing 3 g sodium phenylbutyrate and 1 g taurursodiol as follows:
    - Carton of 7 single-dose packets (NDC 73063-035-04)
    - Carton of 56 single-dose packets (Carton NDC 73063-035-03), contained in 4 boxes with 14 single-dose packets per box

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Risk in Patients with Enterohepatic Circulation Disorders, Pancreatic Disorders, or Intestinal Disorders:** In patients with disorders that interfere with bile acid circulation, consider consulting with a specialist. Monitor for new or worsening diarrhea in these patients. These conditions may also lead to decreased absorption of either of the components of sodium phenylbutyrate-taurursodiol (Relyvrio).
- **Use in Patients Sensitive to High Sodium Intake:** Sodium phenylbutyrate-taurursodiol (Relyvrio) has a high sodium content. In patients sensitive to salt intake, consider the amount of daily

sodium intake in each dose of sodium phenylbutyrate-taurursodiol (Relyvrio) and monitor appropriately.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

G12.21	Amyotrophic Lateral Sclerosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R): Standardized rubric used to stratify the severity of ALS. The rubric includes assessments of speech, salivation, swallowing, handwriting, evaluation of >50% daily nutrition intake via G-tube, cutting food and handling of utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency. Points are applied in each category from zero (complete loss of function) to +4 (no loss of function). The nutritional intake via G-tube is a yes/no response. Possible total scores are zero to 48 with higher scores indicating better function.

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2024. URL www.clinicalpharmacilogy-ip.com Accessed 3/29/24.
2. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2023. URL http://www.dynamed.com. Accessed 6/1/23.
3. Micromedex Healthcare Series [Internet Database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Accessed 3/29/24.
4. Paganoni S, Macklin EA, Hendrix S, et al. Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis. *N Engl J Med*. 2020;383(10):919-930. doi:10.1056/NEJMoa1916945.
5. Relyvrio (sodium phenylbutyrate-taurursodiol) [package insert]. Amylyx Pharmaceuticals, Inc., Cambridge (MA): September 2022.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/10/24.

GUIDELINE UPDATE INFORMATION:

03/15/23	New Medical Coverage Guideline – Sodium phenylbutyrate-taurursodiol (Relyvrio) for the treatment of amyotrophic lateral sclerosis (ALS).
07/15/23	Review and revision to guideline consisting of editing continuation language to standard terminology and updating references.
05/15/24	Review and revision to guideline consisting of revising the position statement for sodium phenylbutyrate-taurursodiol (Relyvrio) therapy to not be medically necessary and updating references.