Relyvrio (sodium phenylbutyrate/taurursodiol) Prior Authorization with Quantity Limit Program Summary

This program applies to Medicaid.

The BCBS MN Step Therapy Supplement applies to this program for Medicaid.

Requests for an oral liquid form of a drug must be approved if BOTH of the following apply:

1) the indication is FDA approved AND

2) the patient is using an enteral tube for feeding or medication administration

POLICY REVIEW CYCLE

Effective Date	Date of Origin
06-01-2024	03-01-2023

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Relyvrio® (sodium phenylbutyrate-taurursodiol) Powder for oral suspension	Treatment of amyotrophic lateral sclerosis (ALS) in adults		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Amyotrophic Lateral Sclerosis (ALS)	Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is an idiopathic, fatal neurodegenerative disease.(2) It is characterized by loss of motor neurons in the spinal cord, brainstem, and motor cortex.(3) Age of onset is between 58-63 years for sporadic disease and 47-52 years for familial disease, with rapidly decreased incidence after 80 years. The clinical hallmark of ALS is the presence of upper and lower motor neuron (UMN and LMN) features involving brainstem and multiple spinal cord regions of innervation.(2) ALS is a rapidly progressive disease with 50% of patients dying within 30 months of symptom onset, and about 20% of patients survive between 5 years and 10 years after symptom onset. Older age at symptom onset, early respiratory muscle dysfunction, and bulbar-onset disease are associated with reduced survival, whereas limb-onset disease, younger age at presentation, and longer diagnostic delay are independent predictors of prolonged survival. Dysphagia develops in most patients, with consequent weight loss and malnutrition. Respiratory compromise eventually develops in most cases, leading to exertional dyspnea, orthopnea, hypoventilation with resultant hypercapnia, and early morning headaches. Progressive weakening of the respiratory muscles leads to respiratory failure, often precipitated by pneumonia.(2)

	Respiratory function is a critical predictor of survival in ALS. International guidelines recommend the assessment of respiratory function in ALS patients at first visit and every 3 months thereafter.(5) Forced (FVC) and slow (SVC) vital capacities are non-invasive conventional tests used to estimate respiratory function in ALS. Their results depend on age, gender, height, and ethnicity, in addition to the functional integrity of the inspiratory and expiratory muscles. FVC is sensitive to detect hypoventilation in ALS and can be more sensitive in detecting diaphragmatic weakness when performed in the supine position.(6) However, the patient must expel air quickly and forcefully, which may cause fatigue and induce bronchospasm and result in an underestimation of actual lung capacity. SVC is easier for the patient with ALS to perform even in the presence of orofacial paresis because it involves exhalation of air in a slow, gentle manner after a maximal inspiration. FVC and SVC have been shown to be tightly correlated, can be used interchangeably, and decline similarly in ALS (about 2%/month).(6,9) Symptomatic treatments remain the cornerstone for management of patients with ALS. Disease modifying treatment options for ALS are limited. Riluzole is the only agent shown to have any impact on survival in ALS. The American Academy of Neurology (AAN) has recommended that riluzole be offered to slow disease progression in patients with ALS.(2) While Relyvrio has been shown to slow the functional decline in patients with ALS, a positive effect on survival was not noted.(4)
Efficacy	The efficacy of Relyvrio was demonstrated in the CENTAUR study, a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial that evaluated its use in adult patients with ALS (NCT03127514). For inclusion in the study, patients had to have a definite diagnosis of sporadic or familial ALS as defined by the revised El Escorial criteria, with symptom onset within 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 (Intent-to-Treat [ITT] population).(1) Baseline disease characteristics were generally comparable between the two treatment groups; 95% were Caucasian, the median age was 57.7 years, and 68% were males. Thirty percent of patients in the Relyvrio treatment group had bulbar disease onset vs. 21% in the placebo group. On average, patients had been diagnosed with ALS six months prior to baseline with a time since onset of first symptom of approximately 13.5 months. At or prior to study entry, 71% of patients were taking riluzole and 34% were taking edaravone. The average (standard deviation) baseline ALS Functional Rating Scale Revised (ALSFRS-R) total score was 35.7 (5.8) in the Relyvrio treatment group and 36.7 (5.1) in the placebo group. Exclusion criteria included presence of tracheostomy, abnormal liver function (defined as AST and/or ALT greater than 3 times the upper limit of normal), renal insufficiency (defined as serum creatinine greater than 1.5 times the upper limit of normal), poorly controlled arterial hypertension (systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg), pregnancy or breastfeeding, history of cholecystectomy, biliary disease, history of class III/IV heart failure, severe pancreatic or intestinal disorders, the presence of unstable psychiatric disease, cognitive impairment, dementia or substance abuse, and exposure at any time to any biologic under investigation for the treatment of subjects with ALS.(1) 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 ALSFRS-R total scores from baseline to Week 24 in the mITT population. The ALSFRS-R scale consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS (speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency). 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-treated patients compared to placebo-treated patients.(1)

	The Centaur Open Label Extension Study (CENTAUR-OLE) provided extended access to patients and assessed the longer-term outcomes for ALS patients who have completed the CENTAUR study.(8) Patients continued to receive Relyvrio for up to 30 months and were allowed continuation of a stable dose of riluzole and/or edaravone. Risk of any key event (i.e., death, tracheostomy, permanent assisted ventilation (PAV), and/or first hospitalization) was 47% lower in those originally randomized to Relyvrio (n=87) versus placebo (n=48, 71% of whom received delayed-start Relyvrio in the OLE phase). Risks of death or tracheostomy/PAV (HR=0.51; 95% CI 0.32 to 0.84; p=0.007) and first hospitalization (HR=0.56; 95% CI 0.34 to 0.95; p=0.03) were also decreased in those originally randomized to Relyvrio. Early administration of Relyvrio in the phase 2 CENTAUR trial prolonged tracheostomy/PAV-free survival and reduced hospitalization risk in ALS, thereby potentially reduced drivers of individual health burden. Adding to the previously reported overall survival and functional benefits attributable to Relyvrio, these findings support a modifying effect of Relyvrio on disease progression.(7)
Safety	Relyvrio has no boxed warnings or contraindications.(1)

REFERENCES

Number	Reference
1	Relyvrio prescribing information. Amylyx Pharmaceuticals Inc. September 2022.
2	Kiernan M. C., Vucic S., Cheah B. C., Turner M. R., Eisen A., Hardiman O., et al. (2011). Amyotrophic lateral sclerosis. *Lancet* 377 942–955. DOI: 10.1016/S0140-6736(10)61156-7.
3	Miller R.G., Jackson C.E., Kasarskis E.J., England J.D., Forshew D., Johnston W., Kalra S., Katz J.S., Mitsumoto H., Rosenfeld J., et al. Practice parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): Report of the Quality Standards Subcommittee of the American of Neurology. Neurology. 2009;73:1227–1233.
4	Paganoni S., Macklin E.A., et al. Trial of Sodium Phenylbutyrate–Taurursodiol for Amyotrophic Lateral Sclerosis. N Engl J Med 2020;383:919-30. DOI: 10.1056/NEJMoa1916945.
5	EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis. Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, et al.. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)–revised report of an EFNS task force. Eur J Neurol. (2012) 19:360–75.
6	Pinto S, de Carvalho M. SVC Is a Marker of Respiratory Decline Function, Similar to FVC, in Patients With ALS. Front Neurol. 2019 Feb 28;10:109. doi: 10.3389/fneur.2019.00109.
7	Paganoni S, Hendrix S, Dickson SP, et al. Effect of sodium phenylbutyrate/taurursodiol on tracheostomy/ventilation-free survival and hospitalization in amyotrophic lateral sclerosis: long-term results from the CENTAUR trial. Journal of Neurology, Neurosurgery & Psychiatry 2022;93:871-875.
8	Open Label Extension Study of AMX0035 in Patients With ALS (CENTAUR-OLE). Amylyx Pharmaceuticals Inc. 2022. https://clinicaltrials.gov/study/NCT03488524.
9	Andrews JA, Meng L, Kulke SF, et al. Association Between Decline in Slow Vital Capacity and Respiratory Insufficiency, Use of Assisted Ventilation, Tracheostomy, or Death in Patients With Amyotrophic Lateral Sclerosis. JAMA Neurol. 2018;75(1):58–64. doi:10.1001/jamaneurol.2017.3339.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Relyvrio	sodium phenylbutyrate-taurursodiol powd pack	3-1 GM	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Relyvrio	Sodium Phenylbutyrate-Taurursodiol Powd Pack	3-1 GM	1	Box	28	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Relyvrio	sodium phenylbutyrate-taurursodiol powd pack	3-1 GM	Medicaid

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Relyvrio	Sodium Phenylbutyrate-Taurursodiol Powd Pack	3-1 GM	Medicaid

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

Initial Evaluation

Target Agent(s) will be approved when ONE of the following is met:

1. ALL of the following:
   - A. The patient has a diagnosis of amyotrophic lateral sclerosis (ALS) [also known as Lou Gehrig's disease] **AND**
   - B. BOTH of the following:
     1. The requested agent will be or was started within 18 months of symptom onset **AND**
     2. The patient has a baseline percent predicted forced vital capacity (FVC) or slow vital capacity (SVC) greater than 60% **AND**
   - C. If the patient has an FDA labeled indication, then ONE of the following:
     1. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
     2. There is support for using the requested agent for the patient's age for the requested indication **AND**
   - D. The patient is able to perform most activities of daily living, defined as scores of 2 points or better on each individual item of the ALS Functional Rating Scale-Revised [ALSFRS-R] **AND**
   - E. ONE of the following:
     1. BOTH of the following:
        - A. The patient is currently treated with riluzole **AND**
        - B. The patient will continue riluzole in combination with the requested agent **OR**
     2. The patient's medication history includes riluzole AND ONE of the following:
        - A. The patient has had an inadequate response to riluzole **OR**

Module	Clinical Criteria for Approval
	B. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over riluzole **OR** 3. The patient has an intolerance or hypersensitivity to riluzole **OR** 4. The patient has an FDA labeled contraindication to riluzole **OR** 5. The patient is currently being treated with the requested agent as indicated by ALL of the following: A. A statement by the prescriber that the patient is currently taking the requested agent **AND** B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on the requested agent **AND** C. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** 6. The prescriber has provided documentation that riluzole cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** F. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** G. The patient does NOT have any FDA labeled contraindications to the requested agent **OR** 2. If the request is for an oral liquid form of a medication, then BOTH of the following: A. The patient has an FDA approved indication **AND** B. The patient uses an enteral tube for feeding or medication administration **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ONE of the following is met: 1. ALL of the following: A. The patient has been previously approved for the requested agent through the plan's Prior Authorization criteria (Note: patients not previously approved for the requested agent will require initial evaluation review) **AND** B. The patient has had clinical benefit with the requested agent **AND** C. The patient is NOT dependent on invasive ventilation or tracheostomy **AND** D. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** E. The patient does NOT have any FDA labeled contraindications to the requested agent **OR** 2. If the request is for an oral liquid form of a medication, then BOTH of the following: A. The patient has an FDA approved indication **AND** B. The patient uses an enteral tube for feeding or medication administration **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 6 months for initial; up to 12 months for renewal