Clinical Policy: Sodium Phenylbutyrate/Taurursodiol (Relyvrio)

Reference Number: LA.PHAR.584
Effective Date: 09.29.23
Last Review Date: 08.21.24
Line of Business: Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Please note: This policy is for medical benefit

Description
Sodium phenylbutyrate/taurursodiol (Relyvrio™) is coformulation of the compounds sodium phenylbutyrate, a molecular chaperone, and taurursodiol, a Bax inhibitor.

FDA Approved Indication(s)
Relyvrio is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Louisiana Healthcare Connections® that Relyvrio is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Amyotrophic Lateral Sclerosis (must meet all)**:**

1. Authorization is not permitted. Member may not initiate therapy with Relyvrio. The manufacturer has started the process to voluntarily discontinue the marketing authorization for Relyvrio and initiated its removal from the market. Relyvrio will no longer be available for new patients as of April 4, 2024 (*see Appendix F*).

Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: LA.PMN.53 for Medicaid.

II. Continued Therapy

A. Amyotrophic Lateral Sclerosis (must meet all)**:**
1. Currently receiving medication via Louisiana Healthcare Connections benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy (e.g., no tracheostomy or permanent assisted ventilation);
3. If the member wishes to continue using Relyvrio, in consultation with their physician, the member may be authorized for continued therapy up to 1 month after which they can be transitioned to a free drug program per the manufacturer (*see Appendix F*);
4. If request is for a dose increase, new dose does not exceed 6 g sodium phenylbutyrate/2 g taurursodiol (2 packets) per day.

Approval duration: 1 month

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: LA.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – LA.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALS: amyotrophic lateral sclerosis
EMG: electromyography
FDA: Food and Drug Administration
LMN: lower motor neuron
SVC: slow vital capacity
UMN: upper motor neuron disease

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
riluzole (Rilutek®)	50 mg PO BID	100 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: General Information

- Revised El Escorial diagnostic criteria for ALS requires the presence of:
  1. Signs of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination;
  2. Signs of upper motor neuron (UMN) degeneration by clinical examination; and
  3. Progressive spread of symptoms or signs within a region or to other regions, together with the absence of:
     a. Electrophysiological evidence of other disease processes that might explain the signs of LMN and/or UMN degenerations; and
     b. Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs;
- The definitions of ALS diagnoses provided by the revised El Escorial criteria are as follows:

Revised El Escorial criteria	
Clinically definite ALS	Clinical evidence alone of UMN and LMN signs in ≥ 3 regions
Clinically probable ALS	Clinical evidence alone of UMN and LMN signs in ≥ 2 regions with some UMN signs rostral to (above) LMN signs
Clinically probable lab-supported ALS	Clinical signs of UMN and LMN dysfunction in 1 region OR UMN signs in 1 region, and LMN signs defined by EMG criteria in ≥ 2 regions
Clinically possible ALS	Clinical signs of UMN and LMN dysfunction in 1 region OR Isolated UMN signs in ≥ 2 regions OR LMN signs rostral to UMN signs

Appendix E: Riluzole Co-administration

There is support for the co-administration of riluzole in ALS:

- The 2009 American Academy of Neurology ALS guideline for the care of the patient with ALS (reaffirmed February 2023) recommends that riluzole should be offered to slow disease progression (Level A).
- The 2020 Canadian best practice recommendations for the management of ALS state the following: riluzole has demonstrated efficacy in improving survival in ALS (level A), there is evidence that riluzole prolongs survival by a median duration of 3 months (level A), and riluzole should be started soon after the diagnosis of ALS (expert consensus).
- Additionally, approximately 71% of patients in the phase 2 CENTAUR trial were receiving concomitant riluzole.

Appendix F: Withdrawal of Relyvrio from the US Market

- On April 4, 2024, Amylyx Pharmaceuticals announced the decision to voluntarily discontinue the marketing authorization for Relyvrio and remove the product from the market based on topline results from the phase 3 PHOENIX trial. PHOENIX did not meet its primary endpoint of reaching statistical significance ($p = 0.667$) as measured by change from baseline in the Revised ALS Functional Rating Scale (ALSFRS-R) total score at Week 48, nor was there statistical significance seen in secondary endpoints. Relyvrio will no longer be available for new patients as of April 4, 2024.
- Action required for prescribers: physicians should not initiate new treatment with Relyvrio, effective April 4, 2024. Patients currently on therapy who, in consultation with their physician, wish to stay on treatment can be transitioned to a free drug program.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
ALS	1 packet (3 g sodium phenylbutyrate and 1 g taurursodiol) daily for the first 3 weeks, followed by 1 packet twice daily thereafter	2 packets (6 g sodium phenylbutyrate and 2 g taurursodiol) per day

VI. Product Availability

Powder for oral suspension: 3 g of sodium phenylbutyrate and 1 g of taurursodiol in single dose packet

VII. References

1. Relyvrio Prescribing Information. Cambridge, MA: Amylyx Pharmaceuticals; September 2022. Available at: https://www.relyvrio.com. Accessed January 12, 2024.
2. Paganoni S, Macklin EA, Hendrix S, et al. Trial of sodium phenylbutyrate-taurursodiol for amyotrophic lateral sclerosis. N Engl J Med. 2020 Sep 3;383(10):919-930.
3. Paganoni S, Hendrix S, Dickson SP, et al. Long-term survival of participants in the CENTAUR trial of sodium phenylbutyrate-taurursodiol in amyotrophic lateral sclerosis. Muscle Nerve. 2021 Jan;63(1):31-39.

4. Paganoni S, Hendrix S, Dickson SP, et al. Effect of sodium phenylbutyrate/taurursodiol on tracheostomy/ventilation-free survival and hospitalisation in amyotrophic lateral sclerosis: long-term results from the CENTAUR trial. J Neurol Neurosurg Psychiatry. 2022;93(8):871-875.
5. Brooks BR, Miller RG, Swash M, et al. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000 Dec;1(5):293-9.
6. Shoesmith C, Abrahao A, Benstead T, et al. Canadian best practice recommendations for the management of amyotrophic lateral sclerosis. CMAJ. 2020 Nov;192(46):E1453-E1468.
7. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009 Oct 13 (reaffirmed February 2023);73(15):1218-26.
8. Amylyx Pharmaceuticals press release. Amylyx pharmaceuticals announces formal intention to remove Relyvrio®/Albrioza™ from the market; provides updates on access to therapy, pipeline, corporate restructuring, and strategy. Available at: https://www.amylyx.com/news/amylyx-pharmaceuticals-announces-formal-intention-to-remove-relyvrior/albriozatm-from-the-market-provides-updates-on-access-to-therapy-pipeline-corporate-restructuring-and-strategy. Accessed April 4, 2024.

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Policy created	05.01.23	08.28.23
Annual review; no significant changes; references reviewed and updated.	04.05.24	07.10.24
Updated Appendix D table of revised El Escorial criteria; references reviewed and updated; removed initial approval criteria and limited continued authorization to 1 month due to manufacturer withdrawal; added Appendix F with details of market withdrawal	08.21.24	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

CLINICAL POLICY
Sodium Phenylbutyrate/Taurursodiol

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. LHCC retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom LHCC has no control or right of control. Providers are not agents or employees of LHCC.

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