

Drug Class Update with New Drug Evaluation: Amyotrophic lateral sclerosis

Date of Review: April 2023

Date of Last Review: Class N/A; Edaravone Injection July 2018

Dates of Literature Search: 04/30/2018-11/10/2022 Edaravone
01/01/2012-11/10/2022 ALS class
No start to 01/18/23 RELYVRIO

Generic Name: sodium phenylbutyrate and taurursodiol

Brand Name (Manufacturer): RELYVRIO (Amylyx Pharmaceuticals)

Dossier Received: no

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

To review new evidence for efficacy and harms of the combination product, sodium phenylbutyrate and taurursodiol, in the treatment of amyotrophic lateral sclerosis (ALS). This review will also evaluate the evidence for other agents approved to treat ALS and update prior authorization criteria as needed.

Plain Language Summary:

- This review looks at new evidence for medicines that are used for amyotrophic lateral sclerosis, also known as Lou Gehrig's disease.
- Amyotrophic lateral sclerosis is a condition that makes a person's muscles weaker, until it becomes difficult to walk and breathe. People with amyotrophic lateral sclerosis usually live for about 2 to 5 years once diagnosed with this condition.
- Three medicines are Food and Drug Administration approved to treat amyotrophic lateral sclerosis. These are riluzole, edaravone, and the new medication sodium phenylbutyrate-taurursodiol. Riluzole is the oldest medicine and evidence shows it may help a person live 2-3 months longer.
- A recent summary of older evidence shows that edaravone may help to slow down how quickly amyotrophic lateral sclerosis makes a person sick.
- A new medicine, sodium phenylbutyrate-taurursodiol (RELYVRIO), has been approved by the Food and Drug Administration to treat amyotrophic lateral sclerosis. Evidence shows it may slow down how quickly amyotrophic lateral sclerosis makes a person sick.
- The Drug Use Research and Management group recommends riluzole be available for use.
- The Drug Use Research and Management group recommends providers explain why someone needs edaravone and sodium phenylbutyrate-taurursodiol before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the efficacy of sodium phenylbutyrate-taurursodiol compared to placebo or currently available treatments for amyotrophic lateral sclerosis (ALS)?
2. What is the safety of sodium phenylbutyrate-taurursodiol for treatment of ALS?
3. What is the comparative efficacy and safety of agents approved for ALS?
4. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed by treatment with a specific agent for ALS?

Conclusions:

- This update includes information from one high-quality systematic review¹ and one randomized control trial.²
- There is low-quality evidence from a Canadian Agency for Drugs and Technologies in Health (CADTH) review that edaravone reduces the change in ALS Functional Rating Scale-Revised (ALSFRS-R) over 6 months. A CADTH common drug review¹ of 3 randomized controlled trials (RCTs) and 1 extension study of edaravone found no evidence that showed a reduction in mortality or improvement of the survival study of death, disability of independent ambulation, loss of upper-limbs function, tracheotomy, use of respirator, use of tube feeding, and loss of useful speech. Only one RCT (Study 19) showed a statistically significant reduction in the change in ALSFRS-R slope over 6 months (between group least squares [LS] mean difference 0.47, 95% confidence interval [CI] 0.19 to 0.74; p=0.001).¹
- Edaravone is available in a new, oral suspension formulation.³
- There is low-quality evidence from one fair-quality phase II trial that sodium phenylbutyrate-taurursodiol reduced the rate (slope) of decline in the total score on the ALSFRS-R from baseline to week 24 compared to placebo (sodium phenylbutyrate-taurursodiol -1.24 points/month vs. placebo -1.66 points/month; difference 0.42 points/month; 95% CI 0.03 to 0.81; p=0.03) in patients with definite ALS.² A minimum clinically important difference (MCID) is not established for this endpoint, though experts have stated a difference of at least 2 points over a 6 month period for most patients would be considered clinically meaningful if reproduced in multiple studies.¹ Trial is downgraded for attrition bias. Additionally, there are concerns related to statistical assumptions with handling of missing data in light of functional status primary endpoint which does not account for mortality.²
- There is insufficient long-term evidence on safety of sodium phenylbutyrate-taurursodiol. Rates of serious adverse events were similar when compared with placebo (12% vs. 19%) at 24 weeks. There were 5 deaths in sodium phenylbutyrate-taurursodiol group and 2 in the placebo group (2:1 randomization).²
- There is insufficient direct comparative evidence for agents in this class.
- Previous evidence has shown riluzole may prolong survival by 2-3 months.⁴
- Evidence for edaravone is primarily limited to a Japanese population¹ and evidence for riluzole is primarily from a White population.² There is insufficient evidence on efficacy or harms data for other subgroups.

Recommendations:

- Designate at least one riluzole formulation as preferred on the preferred-drug list (PDL).
- Designate edaravone and sodium phenylbutyrate-taurursodiol as non-preferred on the PDL.
- Implement prior authorization (PA) criteria for sodium phenylbutyrate-taurursodiol and update edaravone PA criteria as proposed (**Appendix 5**)
- After evaluation of costs in executive session, designate riluzole tablets as preferred and other products as non-preferred.

Summary of Prior Reviews and Current Policy

- A new drug evaluation (NDE) for edaravone injection was presented to the Pharmacy and Therapeutics (P & T) committee in July 2018. The NDE of edaravone evaluated Study 19 in detail.⁵ The NDE found:
 - There is insufficient evidence to determine if edaravone has any significant impact on functional status or disease progression in all ALS patients beyond 6 months.
 - There is insufficient evidence to evaluate the long-term safety of edaravone.
 - There is insufficient evidence to compare edaravone to any other ALS therapies or in specific subpopulations other than Japanese patients.
- Both edaravone formulations (oral and injection) are subject to PA criteria and require concurrent use of riluzole if no contraindication or intolerance.
- Neither riluzole nor edaravone have a status designated on the PDL.

Background:

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's or Charcot's disease, is the most common degenerative and fatal motor neuron disease.⁶ There is increased awareness that frontal and temporal lobes are involved, in addition to motor neurons, in a subset of patients.⁷ The incidence is roughly 1-2 per 100,000 and prevalence of 10-12 per 100,000 in the United States (US) and Europe.⁸ Men are usually twice as commonly affected as women.⁸ ALS symptoms typically do not develop until 50 years of age, and the disease is usually diagnosed between 55 and 65 years of age. Although there is variation in ALS presentation and progression, the average life expectancy is two to five years from the time of diagnosis.⁹ Only about 10-15% of ALS patients live more than 10 years from disease onset, and 50% survive 30 months from symptom onset.⁸ Diagnosis is made using medical history, physical examination, electrodiagnostic testing, and neuroimaging studies to rule out other neurological conditions such as myasthenia gravis or adult onset spinal muscular atrophy.⁸ The revised El Escorial criteria are used most often, though more commonly in clinical trials than clinical practice.⁸ The El Escorial criteria is a diagnostic scale based on locations of motor neuron dysfunction rather than a severity rating. ALS is classified as clinically definite, probable, laboratory-supported probable, possible, and suspected.⁸ Other classification systems including Awaji criteria, which has low test-retest reliability, or the simplified 2019 Gold Coast Criteria, which awaits validation.⁸ Genetic testing may be used in those with family history. Early stages of ALS are marked by muscle stiffness, asymmetric limb weakness, cramping and fatigue.¹⁰ Twenty percent of ALS patients exhibit bulbar symptoms such as slurred speech and dysphagia.¹¹ As ALS progresses, selective degeneration of upper and lower motor neurons eventually results in loss of coordination and muscle strength leading to complete paralysis, respiratory failure, and death.¹¹ Up to 30% of ALS patients may experience significant cognitive or psychological impairment as well as depression and mood imbalance.¹² Subtypes of ALS are progressive bulbar palsy, limb-onset ALS, progressive muscular atrophy, and upper motor neuron predominant ALS.⁷ Cognitive impairment may be present in 45% of patients with ALS.⁷ ALS diagnosis allows Medicare coverage for disability without a 24-month waiting period.¹³ Based on claims data, Oregon Medicaid has over 100 identified cases of ALS, with about 20% of them in the Fee-for-Service (FFS) program. Roughly two-thirds of persons with ALS are Medicare dual enrolled, and approximately half of dual enrolled members are age 65 years or older.

The etiology of ALS is largely unknown, however, mitochondrial abnormalities, signs of oxidative stress, and elevated 3-nitrotyrosine and protein carbonyl levels have been observed in many patients diagnosed with ALS.^{6,14} Established risk factors for development of ALS are age and family history. Sporadic ALS generally affects individuals in their late 50s to early 60s. Only 10-15% of ALS cases are familial ALS, also called genetic⁸, and typically emerge a decade earlier in patients aged in their 40's and 50's.^{9,14} There are no clinical laboratory tests that confirm diagnosis of nongenetically determined ALS.¹⁰

There is no cure for ALS and effective management is primarily focused on symptomatic and supportive care for the patient's physical, emotional and psychological needs.¹⁵ Therapy outcomes which are of clinical value to ALS patients include mobility, muscle strength, quality of life, disease progression, and

mortality. A variety of tools and clinical measures have been employed to manage and monitor ALS patients at various stages of functional decline.^{15,16} Guidelines from the American Academy of Neurology (AAN) recommend noninvasive ventilation (NIV) and percutaneous endoscopic gastrostomy (PEG) as important but underutilized treatments for ALS patients.¹⁵ Noninvasive ventilation may be useful at earlier stages of ALS for the treatment of respiratory insufficiency in order to lengthen survival, slow forced vital capacity decline, and improve patient quality of life.¹⁷ Spirometry with forced vital capacity (FVC) has been commonly used to diagnose diaphragmatic weakness and symptom progression in ALS patients.^{8,17} Slow vital capacity (SVC) is the maximal amount of air exhaled in a relaxed expiration. Testing of FVC is recommended every 3-6 months, FVC < 50% may indicate imminent respiratory failure.¹⁸ Respiratory system dysfunction is often the terminal event for ALS patients. Tracheostomy placement ranges from 2% to 15% and varies by country.¹⁸ Due to the loss of motor function, the majority of patients will eventually require assistance with activities of daily living (ADL).¹⁷ Surgically placed feeding tubes (e.g. PEG tubes) have been used for nutrition to help stabilize patient weight and prolong survival.¹⁵

The ALSFRS-R is a tool widely used by clinicians to assess disease progression in ALS patients.¹⁹ There are 12 items in 4 subdomains of bodily function including bulbar, fine motor, gross motor, and breathing.² Each is scored from 0, indicating total loss of function to 4, indicating no loss of function.² The ALSFRS-R enables clinicians to score the patient's physical function on a scale from 0 (worst) to 48 (normal).¹⁹ The ALSFRS-R has been considered by some to be an improvement over the original ALSFRS due to its incorporation of 3 additional questions regarding dyspnea, orthopnea, and the need for respiratory support.^{19,20} Some studies have used changes in the ALSFRS-R to make survival predictions.²¹ However, there has been criticism regarding use of the ALSFRS-R scale because it may not be sensitive to heterogeneity in ALS disease progression especially among multiple domains over short time periods.^{16,19} An additional validity concern of the ALSFRS-R is its reduced sensitivity for detection of change in low-functioning ALS patients as well as the potential for scores to be affected by mood or effort.^{16,22} The MCID on the ALSFRS-R score is unclear,²² although clinical experts with CADTH have stated a difference of at least 2 points over a 6 month period for most patients would be considered clinically meaningful if reproduced in multiple studies.¹ Changes in the ALSFRS-R have been correlated with patient-perceived changes of physical, emotional, and social function, but patients may be unable to perceive an intervention effect until its impact on the ALSFRS-R is 9 points or more.²³ Clinical trials have shown that the ALSFRS-R declines at a rate of -0.92 units per month in ALS patients.²⁴ Surveys of clinicians estimate that an ALSFRS-R slope change (score vs. time) by 20-25% or more would be considered clinically meaningful.²⁴

Pharmacological treatment options to slow disease progression are few, and there is no evidence that familial ALS or sporadic ALS patients respond better to any particular available therapy.²⁵ Gamma aminobutyric acid (GABA) modulators and recombinant human insulin-like growth factor-1 (IGF-1) have been studied to assess improved function or survival in adult ALS patients, but there is insufficient evidence available to support use of either agent to mitigate the degenerative effects of the disease.²⁵⁻²⁷ Riluzole (1995)²⁸ and edaravone (injection 2017, oral suspension 2022)³ are currently available FDA approved products to manage ALS. The AAN and National Institute for Health and Care Excellence (NICE) guidelines both recommend that riluzole be offered to ALS patients by a neurological specialist to slow disease progression.^{15,29} A 2011 updated Cochrane Review examined the efficacy of riluzole in prolonging survival and in delaying the use of surrogates to sustain survival.³⁰ Evidence from 4 RCTs of acceptable methodological quality with 1477 ALS patients were reviewed.³⁰ Three of the 4 studies with full data on tracheostomy-free survival were compared.³⁰ Riluzole 100 mg per day provided a benefit for the homogeneous group of patients in the first two trials (hazard ratio (HR) 0.80, 95% CI 0.64 to 0.99, P= 0.042).³⁰ The third trial included older patients with more advanced disease, however, the pooled treatment effects were still significant (HR 0.84, 95% CI 0.698 to 0.997, P= 0.046).³⁰ The results indicated that riluzole therapy for ALS patients was associated with an increased median survival benefit from 11.8 to 14.8 months versus placebo, and the author's concluded riluzole 100 mg was reasonably safe and probably prolongs survival by 2 to 3 months in patients with ALS.³⁰ The exact mechanism for the therapeutic benefit of riluzole in ALS has not been determined. Assessment of functional improvement with the ALSFRS-R tool was not performed in riluzole-treated patients.³⁰ Since last review, additional data regarding long-term safety and efficacy of edaravone have been published, though open-label design and post-hoc analyses introduce bias to the results.^{31,32}

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Edaravone Clinical Review Report (CADTH)

A CADTH common drug review of edaravone (RADICAVA, 30 mg/100 mL infusion bag) for use in ALS was published in April 2019.¹ Four RCTs were included: Study 16, Study 18, Study 19 (detailed in previous NDE⁵ from July 2018), and Study 17, which was a parallel-group extension trial of Study 16.¹ All studies were conducted in Japan and were phase III. Enrollment varied in these placebo-controlled trials with Study 16 (n=206) and 17 (n= 206 randomized; n=181 participated) larger than Study 19 (n=137) and Study 18 (n=25).¹ All RCTs included definite or probable ALS cases with varying baseline FVC requirements of greater than 60, 70, or 80%.¹ Primary end point was change in ALSFRS-R for all trials, with other endpoints including time to death or disease progression (e.g. tracheostomy) and additional function and safety endpoints.¹ Concomitant riluzole use was approximately 85-90% for most treatment groups.¹ There were imbalances in study discontinuations between groups and some notable differences in baseline characteristics such as patients with probable versus definite ALS.¹

Table 1. Key efficacy and safety results¹

Outcomes	Study 16		Study 17		Study 18		Study 19	
	PL N=104	ED N=101	ED-PL N=44	ED-ED N=48	PL N=12	ED N=13	PL N=68	ED N=69
Survival analysis for disease progression* Total N (%)	37 (35.6)	38 (37.6)	13 (29.5)	19 (39.6)	4 (33.3)	7 (53.8)	6 (8.8)	2 (2.9)
Death	2 (1.9)	2 (2.0)	1 (2.3)	1 (2.1)	0	1 (7.7)	0	0
P value for log-rank test	0.3814		0.1540		0.1058		0.1284	
P value for generalized Wilcoxon test	0.3992		0.0684		0.0782		0.1415	
ALSFRS-R	PL N=99	ED N=100	ED-PL N=41	ED-ED N=45	PL N=12	ED N=13	PL N=66	ED N=68
Change/month from baseline slope	-1.05 (0.16)	-0.99 (0.16)	-1.62 (0.29)	-0.97 (0.28)	-0.96 (0.3)	-1.14 (0.29)	-1.35 (0.12)	-0.88 (0.12)

LS mean (SE)									
Between group difference LS mean (95% CI)	0.06 (-0.24 to 0.37)		0.66 (-0.09 to 1.41)			-0.18 (-1.02 to 0.66)		0.47 (0.19 to 0.74)	
P value	0.6785		0.0858			0.6614		0.001	
Safety	PL N=104	ED N=102	ED-PL N=45	ED-ED N=48	PL-ED N=88	PL N=12	ED N=13	PL N=68	ED N=69
Subjects with > 0 SAEs N (%)	24 (23.1)	18 (17.6)	13 (28.9)	25 (52.1)	39 (44.3)	2 (16.7)	3 (23.1)	16 (23.5)	11 (15.9)
Deaths, N (%)	2 (1.9)	3 (2.9)	1 (2.2)	4 (8.3)	1 (1.1)	0	1 (7.7)	0	0
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; CI = confidence interval; ED = edaravone; LS = least squares; N = number; PL = placebo; SAEs = serious adverse effects; SE = standard error									
*Death, disability of independent ambulation, loss of upper-limbs function, tracheotomy, use of respirator, use of tube feeding, and loss of useful speech									

Only study 19 demonstrated a statistically significant response in rate of ALSFRS-R decline change from baseline (LS mean difference 0.47; 95% CI 0.19 to 0.74) and differences in survival, respiratory function, and quality of life are not clear.¹ Statistically significant differences were not seen in the other studies. Given the overall natural history of ALS, edaravone should be considered in the majority of ALS patients with preserved respiratory function and functional independence per the authors.¹

After review, 16 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical, non-FDA approved indication), previously included in 2018 DURM review,⁴ or CADTH reviews only detailing CENTAUR trial which is evaluated below.^{33,34}

New Guidelines:

None

After review, 1 guideline³⁵ was excluded due to topic focus (not ALS, non-FDA approved indications).

New Formulations or Indications:

Edaravone (RADICAVA ORS) oral suspension was approved in May 2022 based on pharmacokinetic comparison with an equivalent area under the curve (AUC) and maximum concentration (Cmax) not less than the intravenous infusion at the approved dose.³ It should be used orally or via feeding tube, in the morning after overnight fast and without food consumption for 1 hour after administration due to significant reduction in AUC and Cmax when given with a high-fat meal.³ The daily recommended dose is 105 mg (5mL) and the administration interval mirrors that of RADICAVA intravenous injection with an initial treatment cycle of daily for 14 days, followed by a 14 day drug free period. Subsequent cycles include daily dosing in 10 out of 14 days with a 14 day drug free period.³ Patients may change from intravenous to oral and continue same dosing schedule.³

New FDA Safety Alerts:

None

Randomized Controlled Trials:

A total of 81 citations were manually reviewed from the initial literature search. After further review, 81 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Sodium Phenylbutyrate-taurursodiol (RELYVRIO, previously AMX0035)³⁶ was approved in September 2022 by the FDA for the treatment of ALS in adults.³⁷ Taurursodiol is also known as tauroursodeoxycholic acid³⁷ and the drug combination is known in Canada as sodium phenylbutyrate and ursodocoltaurine (ALBRIOZA).^{33,34,36} Each of the component agents has other therapeutic uses as monotherapy. Sodium phenylbutyrate (BUPHENYL) has FDA approval for treatment of urea cycle disorders, as does the prodrug glycerol phenylbutyrate (RAVICTI).³⁸ Taurursodiol is approved in Italy, China, and Turkey for treatment of bile production disorders, while its metabolite, ursodiol (UDCA) is FDA approved for treatment of primary biliary cirrhosis.³⁸

Clinical Efficacy:

FDA approval was based on CENTAUR (NCT03127514) a phase II, multicenter, double-blind, placebo-controlled, parallel-group RCT evaluating sodium phenylbutyrate 3 g with taurursodiol 1 g administered orally or via feeding tube once daily for 3 weeks, then twice daily, versus placebo over 24 weeks in patients with a diagnosis of definite ALS using the revised El Escorial criteria and SVC exceeding 60% of predicted for age, sex, and height.^{2,39} Riluzole use was allowed if dosing remained stable for a minimum of 30 days before screening.² The protocol was amended in 2017 following FDA approval of edaravone to allow its use before or during the study.^{2,39} An open-label extension study (NCT03488524) to evaluate long-term safety up to 132 weeks has also been completed, results have been reported for secondary efficacy outcomes.⁴⁰⁻⁴² More details on study design and risk of bias are included in **Table 4**.

The study groups were primarily male (69%) and White (95%) with an average age of 57.5 years (n=137).² Baseline score and slope of ALSFRS-R were similar between groups after a 2:1 randomization scheme, though use of concomitant ALS treatments was lower for the sodium phenylbutyrate-taurursodiol group than placebo for riluzole (68% vs. 77%), edaravone (25% vs. 50%) and both (22% vs. 40%).² Bulbar onset of disease was more common with sodium phenylbutyrate-taurursodiol (30%) compared to placebo (21%).²

The primary endpoint was the rate (slope) of decline in the total score on the ALSFRS-R from baseline to week 24.² The sodium phenylbutyrate-taurursodiol group had a -1.24 points/month change compared to -1.66 points/month with placebo (difference 0.42 points/month; 95% CI 0.03 to 0.81; p=0.03).² This calculation relies on an assumption of linearity in ALSFRS-R over time. When using a Mean-By-Visit model which does not rely on linearity the FDA did not find a statistically significant treatment difference (estimated difference 1.86, standard error 1.04; p=0.0749).³⁸ Attrition from drug discontinuation due to adverse events was higher with sodium phenylbutyrate-taurursodiol (19%) versus placebo (8%) and fewer people taking sodium phenylbutyrate-taurursodiol completed the trial drug regimen compared with placebo (69% vs. 77%). Completion of 24-week follow-up was similar between groups (sodium phenylbutyrate-taurursodiol 77% vs placebo 79%). The primary endpoint was calculated using a modified intention to treat (mITT) population which excluded 2 patients who died after randomization and receiving active drug treatment, but who did not have a post-baseline ALSFRS-R score. The analysis uses unverifiable missing data assumptions and may be confounded by patient deaths.³⁸ The primary endpoint is a measure of functional status alone and the risk for attrition bias is high. A

post-hoc joint rank assessment (ranking subjects first by time to death then change from baseline in ALSFRS-R) was performed by the study (rank estimate sodium phenylbutyrate-taurursodiol 72.93 vs. rank estimate placebo 59.07, difference 13.85; p=0.0381). This analysis incorrectly used “last observation carried forward” to account for missing data in a chronic, deteriorating condition. FDA analysis of the joint-rank assessment using multiple-imputation based on a missing at random assumption found no statistical difference in the mITT population (p=0.063) or the ITT population (p=0.079).³⁸ The secondary efficacy outcomes had a hierarchical analysis order and failed to reach statistical significance on the first level, therefore all remaining secondary efficacy analyses (including survival) are considered exploratory.^{2,38}

Risk of bias was generally low other than significant concerns related to attrition and missing data modeling in statistical analysis described above. Racial homogeneity of study population limits applicability to Medicaid population. Concomitant use of existing medications for ALS was low and riluzole use (68-77%) was somewhat lower than in studies with edaravone (~85-90%).¹ Additional research with larger study populations and longer duration with primary survival endpoints in addition to functional outcomes are needed to understand true place in therapy. A phase III study (NCT05021536) with 600 participants is anticipated to conclude in late 2023.⁴³

Clinical Safety:

Serious adverse events occurred in 12% of patients in the sodium phenylbutyrate-taurursodiol group and 19% of patients in the placebo group; all discontinuations due to serious adverse events were considered unrelated to the intervention in both groups (1% vs. 6%).² Discontinuation due to any adverse event were higher for the sodium phenylbutyrate-taurursodiol group (19% total, 15% considered due to intervention) than the placebo group (8% total, 2% considered due to intervention).² There were 7 deaths overall, 5 in the intervention group (including the 2 deaths excluded during the mITT analysis) and 2 in the placebo group.²

The most common adverse reactions which occurred more frequently in the sodium phenylbutyrate-taurursodiol group than the placebo group were gastrointestinal disorders (67% vs. 60%); respiratory, thoracic, and mediastinal disorders (33% vs. 21%); skin and subcutaneous-tissue disorders (18% vs. 17%); metabolism and nutrition disorders (11% vs 8%); cardiac disorders (8% vs. 0%); and eye disorders (6% vs. 2%).² Individual adverse reactions reported more often in phenylbutyrate-taurursodiol treated patients and at least 5% in both groups are in **Table 2**.

Table 2. Adverse Reactions³⁷

Adverse Reaction	Sodium phenylbutyrate-taurursodiol N=89 %	Placebo N=48 %
Diarrhea	25	19
Abdominal pain	21	13
Nausea	18	13
Upper Respiratory tract infection	18	10
Fatigue	12	6
Salivary hypersecretion	11	2
Dizziness	10	4

There are no listed contraindications for sodium phenylbutyrate-taurursodiol.³⁷ There are warnings and precautions against use in patients with enterohepatic circulation disorders, pancreatic disorders, or intestinal disorders because taurursodiol is a bile acid.³⁷ There may be increased risk for diarrhea, as well as altered pharmacokinetics in these patients, so they were excluded from studies.³⁷ There is an additional warning and precaution in patients sensitive to high sodium intake such as people with heart failure, renal impairment, or hypertension.³⁷ Each packet contains 464 mg sodium which would provide 938 mg/day in patients on twice daily maintenance dosing.³⁷

The matching placebo included a number of excipients, including anhydrous sodium phosphate dibasic and sorbitol.³⁹ It is unclear what the total sodium content of placebo would be, or if other excipients contributed to the very high rate of gastrointestinal disorder adverse events seen in the placebo group (60%).²

Look-alike / Sound-alike Error Risk Potential: Ursodiol (ACTIGALL), sodium phenylbutyrate (BUPHENYL), glycerol phenylbutyrate (RAVICTI)

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Survival
- 2) Ventilator/tracheostomy free survival
- 3) Quality of Life
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) ALSFRS-R score (functional status) over 6 months

Table 3. Pharmacology and Pharmacokinetic Properties.³⁷

Parameter	
Mechanism of Action	Unknown
Oral Bioavailability	Sodium phenylbutyrate: Tmax = 0.5 hour; High fat meal reduced Cmax (76%) and AUC (54%) Taurursodiol: Tmax = 4.5 hours, high fat meal did not affect Cmax, increased AUC (39%)
Protein Binding	Sodium phenylbutyrate: 82% Taurursodiol: 98%
Elimination	Sodium phenylbutyrate (~80-100%) excreted in urine within as conjugated phenylacetylglutamine.
Half-Life	Not reported
Metabolism	Phenylactate is major metabolite of phenylbutyrate; ursodiol and glycol-ursodiol are major metabolites of Taurursodiol.

Abbreviations: AUC = area under the curve; Cmax = maximum concentration; Tmax = time to maximum concentration.

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Paganoni S, et al. ^{2,38,39,44} CENTAUR Phase II, RCT, DB, PC	1. sodium phenylbutyrate 3g-taurursodiol 1g 2. placebo (includes multiple excipients) Given once daily for 3 weeks, then twice daily (morning and evening) through week 24 if tolerated. Dissolved in room temperature water and given orally or via feeding tube 2:1 randomization OL extension continued for up to 132 weeks.	<u>Demographics:</u> -Male sex 1. 61 (70%) 2. 32 (67%) -White 1. 82 (94%) 2. 46 (96%) -Bulbar onset 1. 26 (30%) 2. 10 (21%) -Riluzole use 1. 59 (68%) 2. 37 (77%) -Edaravone use 1. 22 (25%) 2. 24 (50%) -Both Riluzole & Edaravone use 1. 19 (22%) 2. 19 (50%) -ALSFRS-R score 1. 35.7 ± 5.8 2. 36.7 ± 5.1 <u>Key Inclusion Criteria:</u> - 18-80 years -ALS by revised El Escorial criteria within 18 mo of onset -SVC > 60% predicted for age, height, and gender -no use of riluzole OR riluzole dose stable for 30 days pre-screening Note: edaravone FDA approved while CENTAUR study ongoing, protocol amended to allow edaravone at time of screening or to start while enrolled in study <u>Key Exclusion Criteria:</u> -presence of tracheostomy -abnormal liver function defined as AST and/or ALT >3x ULN	<u>mITT:</u> 1. 87 2. 48 <u>Attrition:</u> 1. 31% 2. 23% Did not complete trial 24-week follow up	<u>Primary Endpoint:</u> Rate (slope) of decline in total ALSFRS-R from baseline to week 24 1. -1.24 pts/mo 2. -1.66 pts/mo Difference 0.42 pts/month 95% CI 0.03 to 0.81 P=0.03	n/a	<u>Death:</u> 1. 5 (6%) 2. 2 (4%) <u>Serious ADR:</u> 1. 12% 2. 19% <u>Discontinuation due to ADE:</u> 1. 17 (19%) 2. 4 (8%)	n/a	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> (Low) Computer generated permuted block randomization, no stratification. Error in kit distribution gave first 17 participants active drug, and next 9 placebo. Sensitivity analysis excluding these participants yielded similar results to prespecified primary analysis. <u>Performance Bias:</u> (Low) Double-blind with placebo matched to taste, appearance, and dissolution profile. <u>Detection Bias:</u> (Low) ALSFRS-R test given via phone. All ALSFRS-R, VC, and ATLIS evaluators NEALS certified. Blinding maintained throughout trial period. Independent DSMB received blinded and unblinded summary reports. <u>Attrition Bias:</u> (High) High overall attrition, mITT for those who discontinued drug but remained in trial and excluding 2 deaths where patients were randomized to treatment arm and received drug but had no post-baseline ALSFRS-R measurements (first assessment scheduled 21 ± 5 days post-baseline visit). Joint rank analysis primary endpoint (incorporating functional status and mortality) would have been more appropriate per FDA. No imputation performed for missing data, though a sensitivity analysis performed to evaluate effects of missing data. FDA review notes possible confounding of functional endpoints by loss of data due to patient deaths, and that analysis relies on unverifiable missing data assumptions. <u>Reporting Bias:</u> (Low) Protocol published <u>Other Bias:</u> (Unclear) Designed and conducted through NEALS network; collaboration with manufacturer for trial design, data analysis, and manuscript development with confidentiality agreements with authors. FDA statistical review found impact from more influential individual test sites affected overall statistical significance of treatment difference. Additionally, the primary analysis result uses a slope analysis that assumes linearity of ALSFRS-R over time, which is not established.

		<p>-poorly controlled arterial hypertension (SBP>160 mmHg or DBP>100 mmHg)</p> <p>-history of cholecystectomy</p> <p>-Biliary disease which impedes biliary flow</p>							<p>Applicability:</p> <p><u>Patient:</u> Study population primarily White and less representative of disease and Medicaid population as a whole.</p> <p><u>Intervention:</u> Dose appropriate for Phase II trial based on pilot studies.</p> <p><u>Comparator:</u> Placebo appropriate given few treatment options. Therapy with concomitant riluzole (if no contraindication) would be useful as that is current standard of care.</p> <p><u>Outcomes:</u> Functional outcome measure used for short term setting. Information related to clinical outcomes (mortality, QoL, ventilatory-tracheostomy free survival) needed with phase III studies of longer duration.</p> <p><u>Setting:</u> 25 NEALS centers in US</p>
<p>Abbreviations : ADE = adverse drug event; ADR = adverse drug reaction; ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; ALT = alanine transferase; ARR = absolute risk reduction; AST = aspartame transferase; ATLAS = Accurate Test of Limb Isometric Strength; CI = confidence interval; DB = double-blind; DBP = diastolic blood pressure; DSMB = Data Safety and Monitoring Board; FDA = Food and Drug Administration; g = gram; ITT = intention to treat; mITT = modified intention to treat; mmHg = millimeters of mercury; mo = month; N = number of subjects; NA = not applicable; NEALS = Northeast Amyotrophic Lateral Sclerosis Consortium; NNH = number needed to harm; NNT = number needed to treat; OL = open-label; PC = placebo-controlled; pts/mo = points per month; QoL = quality of life; RCT = Randomized controlled trial; SBP = systolic blood pressure; SVC = slow vital capacity; ULN = upper limit of normal; US = United States; VC = vital capacity.</p>									

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Appendix 1: Current Preferred Drug List

<u>Generic</u>	<u>Brand</u>	<u>Route</u>	<u>Form</u>
riluzole	RILUTEK	ORAL	TABLET
edaravone	RADICAVA	INTRAVEN	PIGGYBACK
riluzole	TIGLUTIK	ORAL	ORAL SUSP
riluzole	EXSERVAN	ORAL	FILM
edaravone	RADICAVA ORS	ORAL	ORAL SUSP
riluzole	RILUZOLE	ORAL	TABLET
sod phenylbutyrate/taurursodiol	RELYVRIO	ORAL	POWD PACK

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 10, 2022

<input type="checkbox"/>	# ▲	Searches	Results
<input type="checkbox"/>	1	Riluzole/ae, tu [Adverse Effects, Therapeutic Use]	577
<input type="checkbox"/>	2	Edaravone/ae, tu [Adverse Effects, Therapeutic Use]	110
<input type="checkbox"/>	3	sodium phenylbutyrate.mp.	223
<input type="checkbox"/>	4	taurursodiol.mp.	12
<input type="checkbox"/>	5	3 and 4	12
<input type="checkbox"/>	6	1 or 2 or 5	689
<input type="checkbox"/>	7	limit 6 to (english and (adaptive clinical trial or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or equivalence trial or guideline or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	175
<input type="checkbox"/>	8	Amyotrophic Lateral Sclerosis/dt, th [Drug Therapy, Therapy]	3923
<input type="checkbox"/>	9	limit 8 to (english language and guideline)	6
<input type="checkbox"/>	10	7 or 9	181
<input type="checkbox"/>	11	limit 10 to yr="2012 - 2023"	96

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RELYVRIO safely and effectively. See full prescribing information for RELYVRIO.

RELYVRIO (sodium phenylbutyrate and taurursodiol), for oral suspension

Initial U.S. Approval: 2022

INDICATIONS AND USAGE

RELYVRIO is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage is 1 packet (3 g sodium phenylbutyrate and 1 g taurursodiol) administered orally or via feeding tube as follows: (2.1)
 - Initial dosage: 1 packet daily for the first 3 weeks (2.1)
 - maintenance dosage: 1 packet twice daily thereafter (2.1)
- Empty contents of one packet in a cup containing 8 ounces of room temperature water and stir vigorously prior to administration. (2.2)
- Take within 1 hour of preparation. (2.2)
- Administer RELYVRIO before a snack or meal. (2.2)

DOSAGE FORMS AND STRENGTHS

For oral suspension: 3 g sodium phenylbutyrate and 1 g taurursodiol in single-dose packets (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- 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 RELYVRIO. (5.1)
- Use in Patients Sensitive to High Sodium Intake: RELYVRIO has a high sodium content. In patients sensitive to salt intake, consider the amount of daily sodium intake in each dose of RELYVRIO and monitor appropriately. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (at least 15% and at least 5% greater than placebo) are diarrhea, abdominal pain, nausea, and upper respiratory tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amylyx Pharmaceuticals, Inc. at 877-374-1208 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

See Full Prescribing Information for complete list of clinically significant drug interactions. (7.1, 7.2)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling.

Revised: 09/2022

Appendix 4: Key Inclusion Criteria

Population	Patients with ALS
Intervention	Medications in Appendix 1
Comparator	Medications in Appendix 1, placebo vs. sodium phenylbutyrate-taurursodiol
Outcomes	Mortality or time to permanent ventilation/tracheostomy, functional status, quality of life, adverse reactions
Timing	N/A
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Edaravone (Radicava® or Radicava ORS®)

Goal(s):

- To encourage use of riluzole which has demonstrated mortality benefits.
- To ensure appropriate use of edaravone in populations with clinically definite or probable amyotrophic lateral sclerosis
- To monitor for clinical response for appropriate continuation of therapy.

Length of Authorization:

- Up to 12 months

Requires PA:

- Edaravone (pharmacy and provider administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy of previously approved FFS criteria (after which patient has completed 6-month trial)?	Yes: Go to Renewal Criteria	No: Go to #3
3. Is the diagnosis a FDA approved indication?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is the patient currently on riluzole therapy, OR have a documented contraindication or intolerance to riluzole?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
5. Is the medication being prescribed by or in consultation with a neurologist?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Does the patient have documented percent-predicted forced vital capacity (%FVC) \geq 80%?	Yes: Record lab result. _____ Go to #7	No: Pass to RPh. Deny; medical appropriateness
7. Is there a baseline documentation of the revised ALS Functional Rating Scale (ALSFRS-R) score with \geq 2 points in each of the 12 items?	Yes: Record baseline score. (0 [worst] to 48 [best]) _____ Approve for 6 months based on FDA-approved dosing (Table 1)	No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the prescriber provided documentation that the use of edaravone has slowed in the decline of functional abilities as assessed by a Revised ALS Functional Rating Scale (ALSFRS-R) with no decline more than expected given the natural disease progression (5 points from baseline over 6 months)?	Yes: Go to #2	No: Pass to RPh. Deny; medical appropriateness Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: "Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."
2. Does the patient have documented percent-predicted forced vital capacity (%FVC) \geq 80%?	Yes: Record lab result. Go to #3	No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria

3. Is there a documentation of the revised ALS Functional Rating Scale (ALSFRS-R) score with ≥ 2 points in each of the 12 items?

Yes: Record score.
(0 [worst] to 48 [best])

Approve for 12 months.

No: Pass to RPh. Deny;
medical appropriateness

Table 1. FDA Approved Dosing. (Consult FDA website for prescribing information details at www.fda.gov)

Edaravone (RADICAVA) intravenous solution	Edaravone (RADICAVA ORS) oral suspension
60 mg (two consecutive 30 mg infusion bags) IV infusion over 60 minutes	105 mg (5mL) taking orally or via feeding tube in the morning after overnight fasting. Food should not be consumed for 1 hour after administration except water.
<ul style="list-style-type: none"> • Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period • Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free period 	

P&T/DUR Review: 4/23 (SF); 7/18 (DE)

Implementation: 8/15/18

Sodium Phenylbutyrate/Taurursodiol (Relyvrio™)

Goal(s):

- To encourage use of riluzole which has demonstrated mortality benefits.
- To ensure appropriate use of sodium phenylbutyrate/taurursodiol.

Length of Authorization:

- Up to 12 months

Requires PA:

- All pharmacy claims

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy of previously approved FFS criteria (after which patient has completed 6-month trial)?	Yes: Go to Renewal Criteria	No: Go to #3
3. Is this a FDA approved indication?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is the patient currently on riluzole therapy, OR have a documented contraindication or intolerance to riluzole?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
5. Is the medication being prescribed by or in consultation with a neurologist?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness
6. Does the patient have documented percent-predicted slow vital capacity (%SVC) \geq 60% within past 6 months?	Yes: Record lab result. _____ Go to #7	No: Pass to RPh. Deny; medical appropriateness
7. Is there a baseline documentation of the revised ALS Functional Rating Scale (ALSFRS-R) score?	Yes: Record baseline score. _____ Approve for 6 months based on FDA-approved dosing.	No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the prescriber provided documentation that anticipated decline of functional abilities as assessed by a Revised ALS Functional Rating Scale (ALSFRS-R) has slowed in a clinically meaningful way?	Yes: Got to #2	No: Pass to RPh. Deny; medical appropriateness.

Renewal Criteria

2. Has the patient progressed to permanent ventilation or received a tracheostomy since beginning medication?

Yes: Pass to RPh; Deny; medical appropriateness.

No: Approve for 12 months.

*P&T/DUR Review: 4/23 (SF)
Implementation: 5/1/23*