

## PHARMACY / MEDICAL POLICY – 5.01.578

## Amyotrophic Lateral Sclerosis (ALS) Medications

Effective Date: Mar. 1, 2025

Last Revised: Feb. 11, 2025


Replaces: N/A

RELATED MEDICAL POLICIES:

None

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## Introduction

Amyotrophic lateral sclerosis (ALS)—often called Lou Gehrig disease—is a rare condition. It affects nerve cells that control movements like walking, chewing, and breathing. Because the nerve cells can no longer stimulate muscles, they get weak and paralysis sets in. ALS usually affects people between 40 and 70 years old, although some people develop the condition in their twenties and thirties. Symptoms can start in the arms or legs or in the muscles that control swallowing and speech. Regardless of where the symptoms start, the symptoms advance to other areas of the body. ALS usually is a progressive condition. This means it gets worse over time. The rate of progression—how fast it gets worse—varies from person to person. This policy discusses when certain drugs for ALS may be considered medically necessary.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

Drug	Medical Necessity
<ul style="list-style-type: none"> <li>• <b>Generic edaravone IV</b></li> <li>• <b>Radicava (edaravone) IV</b></li> <li>• <b>Radicava ORS (edaravone) Oral suspension</b></li> </ul>	<p><b>Generic edaravone, Radicava (edaravone), and Radicava ORS (edaravone) may be considered medically necessary when all the following criteria are met:</b></p> <ul style="list-style-type: none"> <li>• The individual has been diagnosed with amyotrophic lateral sclerosis (ALS) based on: <ul style="list-style-type: none"> <li>○ The <b>presence</b> of: <ul style="list-style-type: none"> <li>▪ Evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination</li> </ul> </li> </ul> </li> </ul> <p><b>AND/OR</b></p> <ul style="list-style-type: none"> <li>▪ Evidence of upper motor neuron (UMN) degeneration by clinical examination</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>▪ Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>○ The <b>absence</b> of: <ul style="list-style-type: none"> <li>▪ Electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration</li> </ul> </li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>▪ Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysical signs</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Normal respiratory function is retained (forced vital capacity [FVC] is greater than or equal to 70% of predicted)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Has disease duration of 2 years or less</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Medication is prescribed by or in consultation with a neurologist or ALS specialist</li> </ul>
<p><b>Qalsody (tofersen) Intrathecal</b></p>	<p><b>Qalsody (tofersen) may be considered medically necessary when all the following criteria are met:</b></p> <ul style="list-style-type: none"> <li>• The individual is aged 18 years or older</li> </ul> <p><b>AND</b></p>



Drug	Medical Necessity
	<ul style="list-style-type: none"> <li>• Has been diagnosed with amyotrophic lateral sclerosis (ALS) based on: <ul style="list-style-type: none"> <li>○ The <b>presence</b> of: <ul style="list-style-type: none"> <li>▪ Evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination</li> </ul> </li> <li><b>AND/OR</b> <ul style="list-style-type: none"> <li>▪ Evidence of upper motor neuron (UMN) degeneration by clinical examination</li> </ul> </li> <li><b>AND</b> <ul style="list-style-type: none"> <li>▪ Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination</li> </ul> </li> </ul> </li> <li><b>AND</b> <ul style="list-style-type: none"> <li>○ The <b>absence</b> of: <ul style="list-style-type: none"> <li>▪ Electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration</li> </ul> </li> <li><b>AND</b> <ul style="list-style-type: none"> <li>▪ Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysical signs</li> </ul> </li> </ul> </li> <li><b>AND</b> <ul style="list-style-type: none"> <li>• Has a confirmed mutation in the superoxide dismutase 1 (SOD1) gene</li> </ul> </li> <li><b>AND</b> <ul style="list-style-type: none"> <li>• Functionality is retained for most activities of daily living, defined as a score of 37 or more points on ALS Functional Rating Scale-Revised (ALSFRS-R)</li> </ul> </li> <li><b>AND</b> <ul style="list-style-type: none"> <li>• Slow vital capacity (SVC) of 65% or greater</li> </ul> </li> <li><b>AND</b> <ul style="list-style-type: none"> <li>• Medication is prescribed by or in consultation with a neurologist or ALS specialist</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>• <b>Teglutik (riluzole) Oral suspension</b></li> </ul>	<p><b>Teglutik (riluzole) and Tiglutik (riluzole) may be considered medically necessary for the treatment of amyotrophic lateral sclerosis (ALS) when all the following criteria are met:</b></p>



Drug	Medical Necessity
<ul style="list-style-type: none"> <li><b>Tiglutik (riluzole) Oral suspension</b></li> </ul>	<ul style="list-style-type: none"> <li>The individual is aged 18 years or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has tried generic riluzole tablets first and had an inadequate response or intolerance to generic riluzole tablets</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>Documentation is provided that oral suspension is clinically necessary (e.g., trouble swallowing, etc.)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Medication is prescribed by or in consultation with a neurologist or ALS specialist</li> </ul>

Drug	Investigational
<p><b>As listed</b></p>	<p><b>All other uses of the medications listed in this policy are considered investigational.</b></p> <p><b>The medications listed in this policy are subject to the product’s US Food and Drug Administration (FDA) dosage and administration prescribing information.</b></p>

Length of Approval	
Approval	Criteria
<p><b>Initial authorization</b></p>	<p><b>Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.</b></p> <p><b>All other reviews for Qalsody (tofersen), generic edaravone, Radicava (edaravone), and Radicava ORS (edaravone) may be approved up to 6 months.</b></p> <p><b>All other reviews for Teglutik (riluzole) and Tiglutik (riluzole) may be approved up to 12 months.</b></p>
<p><b>Re-authorization criteria</b></p>	<p><b>Non-formulary exception reviews and all other reviews for re-authorization of all drugs in policy may be approved up to 12 months when the chart notes demonstrate that the individual continues to show a positive clinical response as documented by:</b></p>



## Length of Approval

Approval	Criteria
	<ul style="list-style-type: none"><li>The ability to perform most activities of daily living.</li></ul>

## Documentation Requirements

**The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:**

- Office visit notes that contain the diagnosis, relevant history, physical evaluation, medication history, respiratory function tests, and other relevant information that could support medical necessity consideration

## Coding

Code	Description
<b>HCPCS</b>	
J1301	Injection, edaravone (Radicava), 1 mg
J1304	Injection, tofersen (Qalsody), 1 mg

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

## Related Information

### Benefit Application

Qalsody (tofersen), generic edaravone, and Radicava (edaravone) are managed through the medical benefit. Radicava ORS (edaravone), Teglutik (riluzole), and Tiglutik (riluzole) are managed through the pharmacy benefit.

## Evidence Review



## Radicava (edaravone)

### Clinical Trials

The efficacy of Radicava for the treatment of amyotrophic lateral sclerosis (ALS) was established in a 6-month, randomized, placebo controlled, double-blind study conducted in Japanese individuals with ALS who were living independently and met the following criteria at screening:

1. Functionality retained 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; described below])
2. Normal respiratory function (defined as percent-predicted forced vital capacity values of [%FVC]  $\geq 80\%$ )
3. Definite or Probable ALS based on El Escorial revised criteria
4. Disease duration of 2 years or less

The study enrolled 69 individuals in the Radicava arm and 68 in the placebo arm. Baseline characteristics were similar between these groups, with over 90% of individuals in each group being treated with riluzole.

Radicava was administered as an intravenous infusion of 60 mg given over a 60-minute period according to the following schedule:

- An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period (Cycle 1)
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods (Cycles 2-6)

The primary efficacy endpoint was a comparison of the change between treatment arms in the 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 individuals 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. The decline in ALSFRS-R scores from baseline was significantly less in the RADICAVA-treated individuals as compared to placebo.



## Safety

In randomized, placebo-controlled trials, 184 ALS individuals were administered Radicava 60 mg in treatment cycles for 6 months. The population consisted of Japanese individuals who had a median age of 60 years (range 29- 75) and were 59% male. Most (93%) of these individuals were living independently at the time of screening.

**Table 1** below lists the adverse reactions that occurred in  $\geq 2\%$  of individuals in the Radicava-treated group and that occurred at least 2% more frequently than in the placebo-treated group in randomized placebo-controlled ALS trials. The most common adverse reactions that occurred in  $\geq 10\%$  of Radicava-treated individuals were contusion, gait disturbance, and headache.

**Table 1. Adverse Reactions in Radicava and Placebo-Treated Groups**

Adverse Reaction	Radicava (N=184)	Placebo (N=184)
Contusion	15	9
Gait disturbance	13	9
Headache	10	6
Dermatitis	8	5
Eczema	7	4
Respiratory failure, respiratory disorder, hypoxia	6	4
Glycosuria	4	2
Tinea infection	4	2

## Qalsody (tofersen)

### Clinical Trials

The efficacy of tofersen was studied in a 28-week randomized, double-blind, placebo-controlled trial where 108 individuals with ALS and superoxide dismutase 1 (SOD1) mutation were randomized 2:1 to receive treatment with either tofersen 100mg (n = 72) or placebo (n = 36) for 24 weeks. Participants were allowed to use riluzole and/or edaravone concurrently. These individuals met following inclusion criteria:

1. Slow vital capacity (SVC)  $\geq 65\%$  of the predicted value.



2. Rapid disease progression, defined based on their ALS Functional Rating Scale-Revised (ALSFRS-R)
3. Disease duration of 2 years or less

The primary efficacy endpoint was a comparison of change in the ALSFRS-R total score between the groups from baseline to Week 28. Although individuals in the tofersen group experienced less decline in the ALSFRS-R score than those in the placebo group, the result was not statistically significant. The secondary efficacy endpoint was a comparison of change in plasma NfL and cerebral spinal fluid (CSF) SOD1 protein between the groups from baseline to week 28. The adjusted geometric mean ratio to baseline for NfL in tofersen group was 0.45, which was significantly lower than the placebo arm's ratio of 1.12 with nominal p-value < 0.0001. Similarly, the adjusted geometric mean ratio to baseline for CSF SOD1 protein in treatment group was 0.65, which was significantly lower than the placebo arm's ratio of 0.98 with nominal p-value < 0.0001.

## **Safety**

The most common adverse effects were pain, fatigue, arthralgia, myalgia, and elevated CSF white blood cell. Some of the individuals also experienced less common serious adverse effects, such as myelitis and radiculitis, papilledema, aseptic meningitis, and elevated intracranial pressure.

## **2019 Update**

Reviewed Radicava (edaravone) prescribing information (PI) and conducted a literature search from June 1, 2018, through July 20, 2019. No new evidence found that would change the policy statement. Added information from the El Escorial revised criteria for the diagnosis of ALS. Added a Length of Approval table and removed the Dosage and Quantity Limits table.

## **2020 Update**

Reviewed Radicava (edaravone) PI. Updated the re-authorization criteria based on the progressive nature of the disease removing requirement that the respiratory function remains unchanged. The clinical study in the prescribing information documented slowing the loss of





respiratory function with Radicava treatment as supported by the ALSFRS-R score (includes respiratory function as component of score).

## 2021 Update

Reviewed Radicava (edaravone) PI and conducted a literature search on the management and treatment of ALS. No new information was identified that would require changes to this policy.

## 2022 Update

Review PI and added coverage for Radicava ORS (edaravone) which is an oral suspension formulation. Per the PI the efficacy of Radicava ORS is based on a bioavailability study comparing it to Radicava and Radicava ORS demonstrated an equivalent area under the concentration-time curve (AUC) and similar pharmacokinetics.

## 2023 Update

Review PI and added coverage for Relyvrio (sodium phenylbutyrate and taurursodiol). Reviewed coverage criteria of all drugs in this policy. Added coverage criteria for Qalsody (tofersen) for the adult individuals with indication of ALS with SOD1 gene mutation.

## 2024 Update

Reviewed prescribing information and added coverage criteria for Teglutik (riluzole). Removed Relyvrio (sodium phenylbutyrate and taurursodiol) as it has been withdrawn from the market.

## 2025 Update

Reviewed prescribing information for all drugs in the medical policy. Updated Qalsody (tofersen) criteria removing the requirement the individual has a disease duration of 2 years or less. Added generic edaravone IV to policy with the same policy criteria as Radicava (edaravone) IV. Removed Exservan (riluzole) from the medical policy as the product was withdrawn from the



market on September 30, 2024 by the manufacturer Mitsubishi Tanabe Pharma America, Inc. due to a business decision. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

## References

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## History

Date	Comments
07/01/17	New policy, approved June 13, 2017. Added newly approved agent for ALS.
01/30/18	Minor formatting edits were made to the policy.
07/01/18	Annual Review, approved June 22, 2018. Literature review was conducted from 06/13/2017 to 06/13/2018. Benefit application information was added to reflect medical benefit and no changes to criteria made.
01/01/19	Coding update, added new HCPCS code J1301 (new code effective 1/1/19). Removed HCPCS code J3490.
09/01/19	Annual Review, approved August 13, 2019, effective December 5, 2019. Added information from the El Escorial revised criteria for the diagnosis of ALS.
12/01/20	Annual Review, approved November 19, 2020. Updated re-authorization criteria removing requirement that the respiratory function remains unchanged.
11/01/21	Annual Review, approved October 5, 2021. No changes to policy statements.
08/01/22	Annual Review, approved July 25, 2022. Added Radicava ORS (edaravone) oral suspension to policy with the same coverage criteria as intravenous Radicava.
04/01/23	Interim Review, approved March 14, 2023. Changed title from “Radicava (edaravone)” to “Amyotrophic Lateral Sclerosis (ALS) Medications”. Added coverage for Relyvrio (sodium phenylbutyrate and taurursodiol) for the treatment of ALS in adults. Removed requirements to be diagnosed with definite or probable ALS and to retain functionality for most activities of daily living defined as scores of 2 points or better on each individual item of the ALS Functional Rating Scale – Revised [ALSFRRS-R] for Radicava (edaravone) and Radicava ORS (edaravone) criteria. Updated requirement to have normal respiratory function retained defined as 70% or greater of predicted FVC from 80% or greater of predicted FVC for Radicava (edaravone) and Radicava ORS (edaravone) criteria. Added prescriber requirement to Radicava (edaravone) and



Date	Comments
	Radicava ORS (edaravone) criteria. Changed the wording from "patient" to "individual" throughout the policy for standardization.
06/01/23	Annual Review, approved May 9, 2023. Added coverage criteria for Qalsody (tofersen) for adult individuals with indication of ALS with SOD1 gene mutation. Added J3490 to report Qalsody.
07/01/23	Interim Review, approved June 26, 2023. Updated age requirement of 18 years or older for Qalsody criteria to match FDA label.
10/01/23	Coding update. Added new HCPCS code C9157.
11/01/23	Interim Review, approved October 10, 2023. Added coverage for Exservan (riluzole) and Tiglutik (riluzole) for the treatment of ALS.
01/01/24	Coding update. Added new HCPCS code J1304 and termed HCPCS code C9157.
05/01/24	Annual Review, approved April 9, 2024. Added coverage criteria for Teglutik (riluzole).
07/01/24	Interim Review, approved June 24, 2024. Removed Relyvrio (sodium phenylbutyrate and taurursodiol) as it has been withdrawn from the market.
03/01/25	Annual Review, approved February 11, 2025. Updated Qalsody (tofersen) criteria removing the requirement the individual has a disease duration of 2 years or less. Added generic edaravone IV to policy with the same policy criteria as Radicava (edaravone) IV. Removed Exservan (riluzole) from policy as product has been discontinued. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2025 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

