

# Pharmacy Management Drug Policy

**SUBJECT: Amyotrophic Lateral Sclerosis (ALS)**

**POLICY NUMBER: PHARMACY-111**

**EFFECTIVE DATE: 05/11/2023**

**LAST REVIEW DATE: 05/30/2023**

*If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. This drug policy applies to the following line/s of business:*

## Policy Application

Policy Application		
<b>Category:</b>	<input checked="" type="checkbox"/> Commercial Group (e.g., EPO, HMO, POS, PPO)	<input checked="" type="checkbox"/> Medicare Advantage
	<input checked="" type="checkbox"/> On Exchange Qualified Health Plans (QHP)	<input type="checkbox"/> Medicare Part D
	<input checked="" type="checkbox"/> Off Exchange Direct Pay	<input checked="" type="checkbox"/> Essential Plan (EP)
	<input checked="" type="checkbox"/> Medicaid & Health and Recovery Plans (MMC/HARP)	<input checked="" type="checkbox"/> Child Health Plus (CHP)
	<input type="checkbox"/> Federal Employee Program (FEP)	<input type="checkbox"/> Ancillary Services
	<input checked="" type="checkbox"/> Dual Eligible Special Needs Plan (D-SNP)	

## **DESCRIPTION:**

**Amyotrophic Lateral Sclerosis (ALS)** is a rare neurodegenerative condition characterized by progressive muscle weakness and wasting (atrophy). Over time, patients lose the control of voluntary muscles used for walking, talking, eating, and breathing. ALS is ultimately fatal, typically due to respiratory failure, usually within five years from time of symptom onset.<sup>1</sup>

It is estimated that 30,000 people in the United States are affected by ALS and around 5,000 patients are newly diagnosed each year. In majority of cases there is no family history of the disease (sporadic) but approximately 10% of cases are hereditary (familial). A variety of genes have been linked to the disease. The two most common mutations involving the C9ORF72 gene or superoxide dismutase 1 (SOD1) gene, make up almost 50% of familial ALS cases.<sup>2</sup>

Diagnosis of ALS involves a thorough patient history, neurological examination, and a comprehensive series of tests to rule out other conditions. Common classification criteria used for clinical diagnosis of ALS includes the El Escorial and Awaji criteria. Genetic testing may also be useful, particularly in patients with suspected familial ALS.<sup>3</sup>

ALS treatment involves a multidisciplinary approach to manage symptoms, provide supportive care, and slow the progression of the disease. Symptom management may involve antispastic agents such as muscle relaxants, treatments for muscle cramping, and drugs that target excessive salivation. Physical and occupational therapy are important methods to maintain physical mobility while difficulties swallowing, or speaking, may involve speech-language therapy. As patients develop respiratory muscle weakness, non-invasive and invasive respiratory techniques and devices may be employed.<sup>1-4</sup>

FDA-approved treatments for ALS include riluzole (brand: Rilutek tablets, Exservan oral film, Tiglutik oral suspension), edaravone (brand: Radicava intravenous and Radicava ORS), and sodium phenylbutyrate/taurursodiol (brand Relyvrio). On April 25, 2023, tofersen (brand Qalsody) was FDA approved for the treatment of ALS in adults with the SOD1 gene mutation. Mutations in the SOD1 gene lead to the production of a toxic form of the SOD1 protein, which results in deterioration of motor nerve cells causing progressive muscle weakness. This indication for Qalsody is approved under accelerated approval based on reduction in plasma neurofilament

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light chain and continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

According to the American Academy of Neurology (AAN), riluzole should be offered to slow disease progression in patients with ALS (level A recommendation). The guidelines do not yet address any other FDA-approved agents for the treatment of ALS.<sup>4</sup>

**This policy contains coverage requirements for the following drugs:** Exservan film (riluzole oral film), Tiglutik (riluzole oral suspension), Radicava and Radicava ORS (edaravone), Relyvrio (sodium phenylbutyrate and taurursodiol), and Qalsody (tofersen)

**Tiglutik (riluzole oral suspension) and Exservan film (riluzole oral film)** are indicated for the treatment of ALS. The efficacy for both Exservan and Tiglutik were based upon bioavailability studies compared to oral riluzole tablets.<sup>5,6</sup>

**Radicava and Radicava ORS (edaravone)** is indicated for the treatment of ALS. The approval of Radicava ORS was based on bioavailability data comparing intravenous Radicava and Radicava ORS.<sup>7</sup>

Efficacy of intravenous Radicava was studied in a randomized, placebo-controlled, double-blind study in ALS patients over 6 months. Patients included in the study were required to have functionality retained in most activities of daily living, a percent-predicted forced vital capacity value (% FVC) of  $\geq 80\%$ , definite or probably ALS based on the El Escorial revised criteria, and a disease duration of 2 years or less. Patients were randomized to either Radicava (n=69) or placebo (n=68).<sup>7</sup>

The primary efficacy endpoint was change from baseline in the revised ALS functional rating scale (ALSFERS-R) scores during the 24-week treatment period compared to placebo. When compared to placebo, patients in the Radicava group had statistically significant less decline in the ALSFERS-R score from baseline.

Radicava did not demonstrate clinical benefit in a separate 36-week confirmatory study, in patients with “definite”, “probable” or “probable laboratory-supported” ALS and a longer disease duration of 3 years or less.<sup>8</sup>

**Relyvrio (sodium phenylbutyrate/taurursodiol)** is indicated for the treatment of ALS in adults. The efficacy of Relyvrio was demonstrated in a 24-week, multi-center, randomized, double-blind, placebo-controlled, parallel group study (CENTAUR) trial. 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)  $\geq 60\%$  of predicted at screening. Patients were randomized 2:1 to receive either Relyvrio (n=89) or placebo (n=48) for 24 weeks intent-to-treat [ITT population). The primary analysis involved the modified intent-to-treat (mITT) population, which excluded two early patient deaths, both in the Relyvrio arm (n=135 total mITT population).<sup>9</sup>

The primary efficacy endpoint was the rate of reduction in ALSFERS-R score from baseline to week 24 compared to placebo. There was a statistically significant difference in the rate of reduction in the ALSFERS-R score from baseline to Week 24 favoring the Relyvrio treated group.

In a post-hoc, long-term, intention-to-treat survival analysis, patients originally randomized to Relyvrio had longer median overall survival observed than those originally randomized to

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placebo. It should be noted that this was an exploratory analysis and should be interpreted with caution.

**Qalsody (tofersen)** is indicated for the treatment of ALS in adults who have a mutation in the SOD1 gene. This indication is approved under accelerated approval based on reduction in plasma neurofilament light chain (NfL) observed in patients treated with Qalsody. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

The efficacy of Qalsody was evaluated in the 28-week, double-blind, placebo-controlled Phase 3 VALOR study involving patients with weakness attributable to ALS and confirmed SOD1 mutation. A total of 108 patients were randomized to receive treatment with either Qalsody 100 mg (n=72) or placebo (n=36) for 24 weeks (3 loading doses followed by 5 maintenance doses).<sup>10</sup>

The primary analysis population (n=60, mITT) had SVC  $\geq$  65% of predicted value and met criteria for rapid disease progression, defined by their pre-randomization ALSFRS-R decline slope and SOD1 mutation type.

The primary efficacy analysis was change from baseline to Week 28 in the ALSFRS-R total score. While Qalsody demonstrated less decline in the ALSFRS-R compared to placebo at Week 28, the results were not statistically significant.

The secondary endpoints of change from baseline at Week 28 in plasma NfL and cerebrospinal fluid (CSF) SOD1 protein were nominally statistically significant.

After the completion of the 28-week VALOR study, patients had the option to enroll in an open-label extension study. At the 52-week interim analysis, patients previously receiving placebo who initiated Qalsody saw reductions in NfL, similar to those treated with Qalsody in the placebo-controlled period. Earlier initiation of Qalsody was associated with a trend for reduction in ALSFRS-R decline but was not statistically significant. In addition, earlier initiation of Qalsody was associated with a trend toward a reduction in the risk of death or permanent ventilation but was not statistically significant. It is noted in the Qalsody prescribing information that these results should be interpreted with caution given the limitations of data collected outside a controlled trial.

#### **POLICY:**

<b>Exservan- riluzole oral film (Rx) Tiglutik-riluzole oral suspension (Rx)</b>
<ol style="list-style-type: none"><li>1. Must be <math>\geq</math> 18 years of age <b>AND</b></li><li>2. Must be prescribed by or in consultation with a neurologist, or provider that specializes in Amyotrophic Lateral Sclerosis (ALS) <b>AND</b></li><li>3. Must have a diagnosis of ALS <b>AND</b></li><li>4. Provider must attest that patient is unable to swallow generic riluzole tablets</li><li>5. Quantity Limit: 60 oral films/30 days and 600 mL/30 days</li></ol>
<b>Radicava and Radicava ORS – edaravone injection and kit (Rx/Medical)</b>
<ol style="list-style-type: none"><li>1. Must be greater than 18 years of age <b>AND</b></li><li>2. Must be prescribed by or in consultation with a neurologist, or provider that specializes in Amyotrophiclateral sclerosis (ALS) <b>AND</b></li></ol>

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3. According to the prescriber, must have a diagnosis of “definite” or “probable” ALS as determined by revised El Escorial criteria or Awaji criteria (See appendix for criteria) **AND**
4. Must not have tracheostomy (trach) **OR**
5. For patients who have a trach, the provider must attest that the trach is for prevention of aspiration only
6. Radicava will not be covered for any other non-FDA approved indication
7. Initial and recertification requests will be for 6 months at a time. Recertification requires provider attestation that:
  - a. The patient continues to benefit from therapy **AND**
  - b. The patient is not dependent on invasive ventilation or tracheostomy (unless the trach is for prevention of aspiration only).
8. Recommended Dosing:
  - a. IV: 60mg administered as an IV infusion over 60 minutes.
  - b. Oral Suspension: 105 mg (5 mL) taken orally or via feeding tube in the morning after overnight fasting. Food should not be consumed for 1 hour after administration except water.
    - 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
9. Quantity limits for oral suspension:
  - a. 50 mL bottle: 1 per 28 days
  - b. 70 mL bottle: 1 per 365 days

#### **Relyvrio- sodium phenylbutyrate and taurursodiol (Rx)**

1. Must be  $\geq$  18 years of age **AND**
2. Must be prescribed by or in consultation with a neurologist, or provider that specializes in Amyotrophic Lateral Sclerosis (ALS) **AND**
3. According to the prescriber, must have a diagnosis of “definite” or “probable” ALS as determined by revised El Escorial criteria or Awaji criteria (See appendix for criteria) **AND**
4. Must not have tracheostomy (trach) **OR**
5. For patients who have a trach, the provider must attest that the trach is for prevention of aspiration only
6. Relyvrio will not be covered for any other non-FDA approved indication
7. Initial and recertification requests will be for 6 months at a time. Recertification requires provider attestation that:
  - a. The patient continues to benefit from therapy **AND**
  - b. The patient is not dependent on invasive ventilation or tracheostomy (unless the trach is for prevention of aspiration only).
8. Quantity Limit: 56 packets/28 days

#### **Qalsody-tofersen (Medical)**

Based upon our criteria and assessment of the peer-reviewed evidence, the use of Qalsody (tofersen) has not been medically proven to be effective and, therefore, is considered **experimental/investigational** for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene.

The justification for Qalsody (tofersen) to be considered **experimental/investigational** is as follows:

- a. Based upon our assessment of the peer-reviewed medical literature, there is inconclusive evidence that the drug has a definite positive effect on health outcomes.
- b. Based upon our assessment of the peer-reviewed medical literature, there is inconclusive evidence that the drug, over time, leads to improvement in health outcomes (e.g., the beneficial effects of the service outweigh any harmful effects).

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- c. Based upon our assessment of peer-reviewed medical literature, there is inconclusive evidence that the drug provides improvement in health outcomes in standard conditions of medical practice, outside the clinical investigatory settings.

*Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services*

#### **APPENDIX:**

##### **Revised EI Escorial and Awaji diagnostic criteria for amyotrophic lateral sclerosis (ALS)**

1. Progressive Symptoms
2. Lower motor neuron (LMN) signs by region (bulbar, cervical, thoracic, lumbosacral)
  - a. Clinical: weakness, atrophy, fasciculations
  - b. Electromyography (EMG) (limbs: 2 or more muscles innervated by different roots/nerves. Bulbar and thoracic: 1 or more muscles):
    - i. Lower motor neuron loss: fibrillation potentials, positive sharp waves, fasciculation potentials (Awaji only)
    - ii. Reinnervation: large motor units and reduced recruitment
3. Upper motor neuron (UMN) signs by region (bulbar, cervical, thoracic, lumbosacral)
  - a. Clinical: hyperreflexia, spasticity, pathologic reflexes

##### Clinically Possible ALS

- Clinical/EMG evidence of UMN and LMN signs in 1 region **OR**
- Isolated UMN signs in 2 or more regions **OR**
- LMN signs rostral to UMN signs

##### Clinically Probable Laboratory-supported ALS (EI Escorial only)

- Clinical UMN and LMN signs in 1 region and LMN signs in 2 regions.

##### Clinically Probable ALS

- Clinical/EMG evidence of LMN and UMN signs in 2 or more regions
- Some UMN signs necessarily rostral to LMN signs

##### Clinically Definite ALS

- Clinical/EMG evidence of LMN and UMN signs in 3 or more regions.

Reference: Quinn C, Elman L. Amyotrophic lateral sclerosis, and other motor neuron diseases. Continuum 2020; 26:1323.

#### **APPROVAL TIME PERIODS – INITIAL AND RECERTIFICATION REVIEWS:**

1. Unless otherwise stated within the individual drug criteria, approval time periods are listed in the table below
2. Continued approval at time of recertification will require documentation that the drug is providing ongoing benefit to the patient in terms of improvement or stability in disease state or condition. Such documentation may include progress notes, imaging or laboratory findings, and other objective or subjective measures of benefit which support that continued use of the requested product is medically necessary. Also, ongoing use of the requested product must continue to reflect the current policy's preferred formulary [Recertification reviews may result in the requirement to try more cost-effective treatment alternatives as they become available (i.e., generics or other guideline-supported treatment options)] and the requested dose must continue to meet FDA approved or off-label/guideline supported dosing



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<b>Line of Business</b>	<b>Rx Initial approval</b>	<b>Rx Continued approval</b>	<b>Medical Initial approval</b>	<b>Medical Recert</b>
<b>Commercial, Exchange SafetyNet (Medicaid, HARP, CHP, Essential Plan)</b>	6 months (or as stated within individual drug policy)	6 months (or as stated within individual drug policy)	All sites of service –6 months	All sites of service – 6 months
<b>Medicare</b>	Defined in Medicare Drug Policy	Defined in Medicare Drug Policy	All sites of service – 6 months	All sites of service – 6 months

#### **POLICY GUIDELINES:**

1. Prior authorization is contract dependent.
2. This policy is applicable to drugs that are included on a specific drug formulary (RX benefit only). If a drug referenced in this policy is non-formulary, please reference the Non-Formulary Medication Exception Review Policy for review guidelines.
3. Not all contracts cover all Medical Infusible drugs. Refer to specific contract/benefit plan language for exclusions of Injectable Medications.
4. For members with Medicare Part B, medications with a National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) will be covered pursuant to the criteria outlined by the NCD and/or LCD. NCDs/LCDs for applicable medications can be found on the CMS website at <https://www.cms.gov/medicare-coverage-database/search.aspx>. Indications that have not been addressed by the applicable medication's LCD/NCD will be covered in accordance with criteria determined by the Health Plan (which may include review per the Health Plan's Off-Label Use of FDA Approved Drugs policy). Step therapy requirements may be imposed in addition to LCD/NCD requirements.
5. Supportive documentation of previous drug use must be submitted for any criterion that requires the trial of a preferred agent if the preferred drug is not found in claims history.
6. Dose and frequency should be in accordance with the FDA label or recognized compendia (for off-label uses). When services are performed in excess of established parameters, they may be subject to review for medical necessity.
7. For contracts where Insurance Law § 4903(c-1), and Public Health Law § 4903(3-a) are applicable, if trial of preferred drug(s) is the only criterion that is not met for a given condition, and one of the following circumstances can be substantiated by the requesting provider, then trial of the preferred drug(s) will not be required. The provider must make their intent to override a trial of the preferred drugs clear and must provide rationale and supporting documentation for one of the following:
  - The required prescription drug(s) is (are) contraindicated or will likely cause an adverse reaction or physical or mental harm to the member;
  - The required prescription drug is expected to be ineffective based on the known clinical history and conditions and concurrent drug regimen;
  - The required prescription drug(s) was (were) previously tried while under the current or a previous health plan, or another prescription drug or drugs in the same pharmacologic class or with the same mechanism of action was (were) previously tried and such prescription drug(s) was (were) discontinued due to lack of efficacy or effectiveness, diminished effect, or an adverse event;
  - The required prescription drug(s) is (are) not in the patient's best interest because it will likely cause a significant barrier to adherence to or compliance with the plan of care, will likely worsen a comorbid condition, or will likely decrease the ability to achieve or maintain reasonable functional ability in performing daily activities;
  - The individual is stable on the requested prescription drug. The medical profile of

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the individual (age, disease state, comorbidities), along with the rationale for deeming stability as it relates to standard medical practice and evidence-based practice protocols for the disease state will be taken into consideration.

- The above criteria are not applicable to requests for brand name medications that have an AB rated generic. We can require a trial of an AB-rated generic equivalent prior to providing coverage for the equivalent brand name prescription drug.
8. Some drugs will require prior authorization prior to criteria being added to the policy.

#### **CODES:**

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key:

Experimental/Investigational = (E/I),

Not medically necessary/ appropriate = (NMN).

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#### **HCPCS:**

Drug Name	J-code (if assigned)	NDC
Radicava (injection)	J1301	70510-2171-01 70510-2171-02
Qalsody	Not Assigned	64406-0109-01

#### **UPDATES:**

Date	Revision
05/30/2023	Revised
05/11/2023	Created
05/11/2023	P&T Committee Approval

#### **REFERENCES:**

1. Miller RG, Jackson CE, Kasarskis EJ, 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). *Neurology*. 2009 (reaffirmed 2020);73(15):1227-1233.
2. National Organization for Rare Disorders (NORD). Amyotrophic Lateral Sclerosis. Last Updated February 13, 2023. Available at: <https://rarediseases.org/rare-diseases/amyotrophic-lateral-sclerosis/#complete-report>. Accessed May 11, 2023.
3. Quinn C, Elman L. Amyotrophic lateral sclerosis, and other motor neuron diseases. *Continuum*. 2020; 26:1323

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4. 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). *Neurology*. 2009 (reaffirmed 2023);73:1218-1226.
5. Exservan [package insert]. Jersey City, NJ: Mitsubishi Tanabe Pharma America, Inc; December 2022.
6. Tiglutik [package insert]. Berwyn, PA: Itf Pharma, Inc.; April 2021.
7. Radicava and Radicava ORS [package insert]. Jersey City, NJ: Mitsubishi Tanabe Pharma America, Inc.; December 2022.
8. Abe K, Itoyama Y, Sobue G, et al. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. *Amyotroph Lateral Scler Frontotemporal Degener*. 2014;15(7-8):610-617.
9. Relyvrio [package insert]. Cambridge, MA: Amylyx Pharmaceuticals Inc.;April 2023.
10. Qalsody [package insert]. Cambridge, MA: Biogen Inc.; April 2023.