BlueCross BlueShield Arizona

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**PHARMACY COVERAGE GUIDELINES**
**SECTION: DRUGS**

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# EXSERVAN (riluzole)

**Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.**

**This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.**

**The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.**

**The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.**

**State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.**

**Pharmacy Coverage Guidelines are subject to change as new information becomes available.**

**For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.**



This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

## EXSERVAN (riluzole)

**Criteria**:

- **Criteria for initial therapy:** Exservan (riluzole) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist
  2. Individual is 18 years of age or older
  3. A confirmed diagnosis of **amyotrophic lateral sclerosis (ALS)**
  4. Failure, intolerance, or contraindication to riluzole (generic for Rilutek)
  5. Will not be used in an individual with severe hepatic impairment (Child-Pugh Class C) or baseline elevations of serum transaminases > 5x the upper limit of normal or evidence of liver dysfunction (e.g., elevated bilirubin)

  **Initial approval duration**: 6 months

- **Criteria for continuation of coverage (renewal request):** Exservan (riluzole) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist
  2. Individual's condition responded while on therapy
     a. Response is defined as:
        i. Documented evidence of efficacy, disease stability and/or improvement by continuing to have scores of 2 points or better on each individual item of the ALSFRS-R score or a 20% in ALSFRS-R score
  3. Individual has been adherent with the medication
  4. Individual has not developed any adverse drug effects that may exclude continued use
     a. Significant adverse effect such as:
        i. Hepatic injury
        ii. Interstitial lung disease
        iii. Neutropenia
  5. There are no significant interacting drugs

  **Renewal duration**: 12 months

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- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of a Non-Cancer Medications**

  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

**Description:**

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease and Charcot disease, is a rare disease that affects nerve cells in the brain and the spinal cord leading to progressive muscle weakness and premature death. ALS is also known as motor neuron disease (MND).

The clinical standard for the diagnosis of ALS is the revised El Escorial World Federation of Neurology criteria, also known as the Airlie House criteria. The degree of certainty of the diagnosis is increased by the number of body regions that demonstrate upper motor neuron (UMN) and lower motor neuron (LMN) signs. The body is divided into 4 regions: bulbar (muscles of face, mouth, and throat), cervical (muscles of the back of the head and neck, the shoulders and upper back, and the upper extremities), thoracic (muscles of the chest and abdomen and the middle portion of the spinal muscles), and lumbosacral (muscles of the lower back, groin, and lower extremities). UMN signs are mild weakness, stiffness, spasticity, and abnormally brisk reflexes; LMN signs are progressive muscle weakness, atrophy/wasting, fasciculations, and loss of reflexes and muscle tone.

By the revised El Escorial criteria, the diagnosis of ALS requires evidence of LMN degeneration by clinical, electrophysiological, or neuropathological examination; evidence of UMN degeneration by clinical examination; and the presence of progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination. Hallmark findings in the electrodiagnosis of ALS are normal sensory nerve conduction studies and abnormal motor nerve conduction studies, with reduced motor compound muscle action potentials. The needle exam shows changes characteristic of ongoing denervation and reinnervation of muscles.
The revised El Escorial criteria also requires the absence of electrophysiologic and pathologic evidence of other disease processes that might explain the signs of lower and/or upper motor neuron degeneration, and the absence of neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiologic signs.

In 2008, the Awaji-shima ALS criteria were proposed for the diagnosis of ALS, given that approximately 21% of patients die from ALS without having ever met the El Escorial criteria for the disease. Although similar to the revised El Escorial criteria, the newer Awaji-shima criteria differ by allowing electrodiagnostic and clinical criteria for LMN signs to be combined to determine if a single limb is abnormal, and by permitting fasciculation potentials by needle electromyography to be used as evidence of ongoing denervation in a muscle with evidence of neurogenic change.

The ALS Functional Rating Scale-Revised (ALSFRS-R) is a questionnaire that measures and evaluates the decline in physical function over time. The scale consists of 12 questions that evaluate fine motor, gross motor, bulbar, and respiratory function of individuals with ALS. Items evaluated include 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 ALSFRS-R shows close agreement with objective measures of muscle strength and pulmonary function, good construct validity and is sensitive to change in the patient's condition, and it shows test-retest reliability and is consistent. Therapy that results in a change of at least 20% in the slope of the ALSFRS-r is considered meaningful.

The differential diagnosis is extensive and includes: multifocal motor neuropathy, cervical radiculomyelopathy, benign fasciculations, inflammatory myopathy, post-polio syndrome, monomelic amyotrophy, hereditary spastic paraplegia, spinobulbar muscular atrophy, myasthenia gravis, hyperthyroidism, and others.

There are other forms of motor neuron disease that are considered variants of ALS: progressive muscular atrophy (a progressive disorder that is limited to lower motor neurons), primary lateral sclerosis (a progressive disorder that is clinically limited to the upper motor neurons), progressive bulbar palsy (a progressive upper and lower motor neuron disorder of cranial muscles), flail arm syndrome (presents with progressive lower motor neuron weakness of the arms), flail leg syndrome (presents with slowly progressive, distal lower motor neuron weakness of the legs), and ALS-plus syndrome is the designation for patients who meet the clinical criteria for ALS and also have features of other disorders that exclude the diagnosis of ALS, such as autonomic insufficiency, parkinsonism, supranuclear gaze paresis, and cerebellar ataxia.

Riluzole is an oral medication that acts to slow the progression ALS symptoms and prolong life. It protects motor nerves from further deterioration by reducing glutamate levels in the brain and spinal cord by blocking its release from nerve terminals. Riluzole is available as a 50 mg tablet (generic and as Rilutek), a 50 mg/ao mL suspension (as Tiglutik), and as a 50 mg film (as Exservan).

**Definitions:**

**Adult:** Age 18 years and older

**UMN:** Upper motor neuron

**LMN:** Lower motor neuron

**ALS Association: El Escorial World Federation of Neurology for the diagnosis of ALS:**
***Criteria for the diagnosis of Amyotrophic Lateral Sclerosis:***
The diagnoses of ALS require 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 signs within a region or to other regions, together with the absence of
4) Electrophysiological evidence of other disease processes that might explain the signs of LMN and/or UMN degenerations; and
5) Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

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***Clinical features in the diagnosis of ALS:***

Patients with signs of LMN degeneration (weakness, atrophy/wasting and clinical fasciculation's) and UMN degeneration (spasticity, pathologic reflexes, etc.) may be suspected as having ALS. Careful history, physical and neurological examination must search for further clinical evidence of LMN and UMN signs in four regions of the central nervous system.

***Clinical features required for the diagnosis of ALS:***

1) Signs of LMN degeneration (weakness, atrophy/wasting and clinical fasciculations) in one or more of the four regions (bulbar, cervical, thoracic, lumbosacral). LMN findings in a region are without regard to right or left, but are indicative of the level of neuraxis involved. Therefore, spread of weakness, wasting and fasciculations to another region is more important than spread from right to left or vice-versa.

2) Signs of UMN degeneration (increased or donic tendon reflexes, spasticity, pseudobulbar features, Hoffmann reflex and extensor plantar response) in one or more of the four regions. These UMN signs are clinically appreciated best in the bulbar, cervical and lumbosacral regions. UMN findings in a region are also without regard to right or left. Once the physical and neurological examinations provide information on the presence or absence of LMN and UMN signs in the four regions (bulbar, cervical, thoracic, lumbosacral) they must be ordered topographically in the manner to determine the certainty of the diagnosis of ALS.

3) The topographical location of certain UMN and LMN signs in four regions of the CNS together with progression of these signs determines the certainty of the diagnoses of ALS. Progression is a cardinal feature of the clinical diagnosis of ALS. Progression of signs within a region and progression of signs to involve other regions are crucial to the diagnosis.

Clinical examinations should be repeated at least every six (6) months to assess progression.

Cases which meet the topographical criteria for probable or definite ALS but which lack progression during the twelve (12) month period diagnosis should be designated as possible ALS.

**El Escorial World Federation of Neurology criteria & Awaji-shima criteria:**

***Definite ALS:***

Clinically definite ALS is defined by UMN and LMN signs in the bulbar region and at least 2 of the other spinal regions or in 3 spinal regions

**Awaji-shima** definite ALS is defined by clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions or the presence of LMN and UMN signs in 3 spinal regions

***Probable ALS:***

Clinically probable ALS is defined as UMN and LMN signs in at least 2 regions with UMN in a region above LMN signs

**Awaji-shima p**robable ALS is defined by clinical or electrophysiological evidence by the presence of LMN and UMN signs in at least 2 regions with some UMN signs necessarily rostral to (above) the LMN signs

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***Clinically Probable-Laboratory-Supported ALS:***
Clinically probable-laboratory-supported ALS is defined as UMN and LMN signs in 1 region or UMN signs in 1 region coupled with LMN signs by electromyography (EMG) in at least 2 limbs

***Possible ALS:***
Clinically possible ALS is defined as UMN and LMN signs in 1 body region, or UMN signs alone in at least 2 regions, or LMN signs in regions above UMN signs

**Awaji-shima p**ossible ALS is defined when clinical or electrophysiological signs of UMN and LMN dysfunction are found only in one region or UMN signs are found alone in two or more regions or LMN signs are found rostral to UMN signs

***Clinically Suspected ALS:***
Pure LMN syndrome in 2 or more regions with other causes of LMN disease adequately excluded

***Supportive clinical features:***
Clinical features that support the diagnosis of ALS include one or more of the following:
1) Abnormal pulmonary function test not explained by other causes
2) Abnormal speech studies not explained by other causes
3) Abnormal swallowing studies not explained by other causes
4) Abnormal larynx function studies not explained by other causes
5) Abnormal isokinetic or isometric strength test in clinically uninvolved muscles
6) Abnormal muscle biopsy with evidence of denervation

***Inconsistent clinical features:***
Clinical findings inconsistent with the diagnoses of ALS include one or more of the following not explained by physiological changes associated with aging or other disease processes:
1) Sensory dysfunction
2) Sphincter abnormalities
3) Autonomic nervous system dysfunction
4) Anterior visual pathway abnormalities
5) Movement abnormalities associated with probable Parkinson's disease defined by DATATOP criteria
6) Cognitive abnormalities associated with clinical Alzheimer's disease defined by NINCDS-ADRDA criteria

***Types of ALS:***
The clinical signs of progressive LMN and UMN degeneration seen in ALS may:
a) occur alone (sporadic ALS),
b) be present incidentally with other pre-existing disease processes that have not developed in parallel with the ALS (coexistent sporadic ALS),
c) occur in association with laboratory-defined or epidemiologically defined abnormalities that are time-linked to the ALS (ALS-related syndromes), or
d) occur in association with clinical, genetic or epidemiological features which develop in parallel with the ALS (ALS variants)

A proposed a system of stages, standardized as proportions of elapsed time through the course of ALS. The milestones, and their typical time of occurrence, are as follows:

- Stage 1: Symptom onset (involvement of first region)
- Stage 2A: Diagnosis (35% of the way through the disease course)
- Stage 2B: Involvement of second region (38%)
- Stage 3: Involvement of third region (61%)
- Stage 4A: Need for gastrostomy (77%)
- Stage 4B: Need for noninvasive ventilation (80%)

**The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R):**

An instrument for evaluating the functional status of patients with ALS. It can be used to monitor functional change in a patient over time. The higher the score the more function is retained. Therapy that results in a change of at least 20% in the slope of the ALSFRS-R is considered meaningful.

**Item 1: SPEECH**

4: Normal speech process
3: Detectable speech disturbance
2: Intelligible with repeating
1: Speech combined with non-vocal communication
0: Loss of useful speech

**Item 2: SALIVATION**

4: Normal
3: Slight but definite excess of saliva in mouth; may have nighttime drooling
2: Moderately excessive saliva; may have minimal drooling (during the day)
1: Marked excess of saliva with some drooling
0: Marked drooling; requires constant tissue or handkerchief

**Item 3: SWALLOWING**

4: Normal eating habits
3: Early eating problems – occasional choking
2: Dietary consistency changes
1: Needs supplement tube feeding
0: NPO (exclusively parenteral or enteral feeding)

**Item 4: HANDWRITING**

4: Normal
3: Slow or sloppy: all words are legible
2: Not all words are legible
1: Able to grip pen, but unable to write
0: Unable to grip pen

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**Item 5a: CUTTING FOOD AND HANDLING UTENSILS**
**Patients without gastrostomy: Use 5b if > 50% is through g-tube**
4: Normal
3: Somewhat slow and clumsy, but no help needed
2: Can cut most foods (> 50%), although slow and clumsy; some help needed
1: Food must be cut by someone, but can still feed slowly
0: Needs to be fed

**Item 5b: CUTTING FOOD AND HANDLING UTENSILS**
**Patients with gastrostomy: 5b option is used if the patient has a gastrostomy and only if it is the primary method (> 50%) of eating**
4: Normal
3: Clumsy, but able to perform all manipulations independently
2: Some help needed with closures and fasteners
1: Provides minimal assistance to caregiver
0: Unable to perform any aspect of task

**Item 6: DRESSING AND HYGIENE**
4: Normal function
3: Independent and complete self-care with effort or decreased efficiency
2: Intermittent assistance or substitute methods
1: Needs attendant for self-care
0: Total dependence

**Item 7: TURNING IN BED AND ADJUSTING BED CLOTHES**
4: Normal function
3: Somewhat slow and clumsy, but no help needed
2: Can turn alone, or adjust sheets, but with great difficulty
1: Can initiate, but not turn or adjust sheets alone
0: Helpless

**Item 8: WALKING**
4: Normal
3: Early ambulation difficulties
2: Walks with assistance
1: Non-ambulatory functional movement
0: No purposeful leg movement

**Item 9: CLIMBING STAIRS**
4: Normal
3: Slow
2: Mild unsteadiness or fatigue
1: Needs assistance
0: Cannot do

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**Item 10: DYSPNEA**
4: None
3: Occurs when walking
2: Occurs with one or more of the following: eating, bathing, dressing (ADL)
1: Occurs at rest: difficulty breathing when either sitting or lying
0: Significant difficulty: considering using mechanical respiratory support

**Item 11: ORTHOPNEA**
4: None
3: Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows
2: Needs extra pillows in order to sleep (more than two)
1: Can only sleep sitting up
0: Unable to sleep without mechanical assistance

**Item 12: RESPIRATORY INSUFFICIENCY**
4: None
3: Intermittent use of BiPAP
2: Continuous use of BiPAP during the night
1: Continuous use of BiPAP during day & night
0: Invasive mechanical ventilation by intubation or tracheostomy

**Resources:**

Exservan (riluzole) product information, revised by Mitsubishi Tanabe Pharma America, Inc. 04-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on June 15, 2021.

Rilutek (riluzole) product information, revised by Covis Pharna 03-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on April 07, 2021.

Riluzole product information, revised by Mylan Pharmaceuticals Inc. 08-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on April 07, 2021.

Galvez-Jimenez N, Goyal NA, Cudkowicz ME. Disease-modifying treatment of amyotrophic lateral sclerosis. In: UpToDate, Shefner JM, Goddeau RP (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed on April 07, 2021.

Elman LB, McCluskey L. Diagnosi of amyotrophic lateral sclerosis and other forms of motor neuron disease. In: UpToDate, Shefner JM, Goddeau RP (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed on April 07, 2021.