Riluzole (Rilutek/Tiglutik)
Policy Number: C9697-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
9/1/2016	1/1/2019	1/1/2020
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL**
	RxPA	Q4

PRODUCTS AFFECTED:
Rilutek (riluzole), riluzole, Tiglutik(riluzole)

DRUG CLASS:
ALS Agents

ROUTE OF ADMINISTRATION:
Oral

PLACE OF SERVICE:
Retail Pharmacy

AVAILABLE DOSAGE FORMS:
Riluzole TABS 50MG, Rilutek TABS 50MG, Tiglutik SUSP 50MG/10ML

FDA-APPROVED USES: indicated for the treatment of patients with amyotrophic lateral sclerosis (ALS). Rilutek (riluzole) extends survival and/or time to tracheostomy

COMPENDIAL APPROVED OFF-LABELED USES: None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS: amyotrophic lateral sclerosis

REQUIRED MEDICAL INFORMATION:

A. AMYOTROPHIC LATERAL SCLEROSIS(ALS):
1. (a) Documentation supporting the clinical diagnosis of 'definite ALS' or 'probable ALS' by World Federation of Neurology (WFN) criteria (other causes for progressive muscle atrophy have been excluded)
   AND
   (b) Symptoms present for less than 5 years
   AND
   (c) FVC > 60% predicted
   AND
   (d) Member does not have a tracheostomy
   OR
2. (a) Documentation supporting the clinical diagnosis of 'definite ALS' or 'probable ALS' by World Federation of Neurology (WFN) criteria (other causes for progressive muscle atrophy have been excluded
   AND
   (b) Symptoms present for more than 5 years

AND
(c) FVC <60% predicted
AND
(d) tracheostomy for prevention of aspiration only (ventilator independent)
AND
3. Documentation of aminotransferases prior to therapy and plan documenting liver enzyme monitoring for the first 3 months and periodically thereafter

DURATION OF APPROVAL: Initial authorization: 12 months, Continuation of therapy: 12 months

QUANTITY: maximum dose: 50 mg twice daily.

PRESCRIBER REQUIREMENTS: Prescribed by, or in consultation with, a board-certified neurologist experienced in the management/treatment of amyotrophic lateral sclerosis (ALS). Submit consultation notes if applicable.

AGE RESTRICTIONS: 18 years of age or older

GENDER:
Male and female

CONTINUATION OF THERAPY:
A. AMYOTROPHIC LATERAL SCLEROSIS(ALS):
1. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)
AND
2. Disease stability or mild progression indicating a slowing of decline and patient has not had a tracheostomy since initial authorization
AND
3. Documentation of the patient having follow-up monitoring of a complete blood count (CBC) with differential and liver function tests (LFTs) every month for the first 3 months of therapy and every 3 months thereafter

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION: All other uses of riluzole are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. RILUTEK is of uncertain benefit in patients with: tracheostomy required for ventilation, other incurable life-threatening disorders, and other forms of anterior horn cell disease. The safety and efficacy of RILUTEK have not been studied in motor neuron diseases other than ALS. Therefore, RILUTEK should not be used in any other form of motor neuron disease.

OTHER SPECIAL CONSIDERATIONS: None

BACKGROUND:
Amyotrophic Lateral Sclerosis (ALS)
- Also known as Charcot's disease and Lou Gehrig's disease, is a disease of unknown cause characterized by slowly progressive degeneration of upper motor neurons (UMNs) and lower motor neurons (LMNs).
- An adult-onset, neurodegenerative disease characterized by loss of motor neurons in the spinal cord, brainstem, and motor cortex. ALS primarily affects the upper and lower motor

neurons and is characterized by muscle weakness, disability, and eventual death, usually from respiratory failure.
- Cause of the disease is unknown, and there is no cure.
- One of the most common neuromuscular disease worldwide and affects individuals of all races and ethnic backgrounds (NIND 2017). In 2016 the Centers for Disease Control and Prevention estimated that between 14,000 - 15,000 Americans have ALS.
- Most common in individuals 40-60 years old, but younger and older people can develop the disease. Men are more likely to develop ALS than women. Studies suggest an overall ratio of about 1.5 men to every woman who develops ALS in Western countries (ALS Association Epidemiology of ALS and Suspected Clusters)

A diagnosis of ALS is based upon evidence of upper and lower motor neuron signs, relentless disease progression, and the absence of an alternative etiology (Kiernan MC; Brooks BR; AAN 2009). ALS, as with other motor neuron diseases, does not have a diagnostic test that can confirm or entirely exclude its diagnosis.

ALS management is primarily managed with symptomatic treatment and palliative care. There is no known cure for ALS at the present time. There are currently two FDA approved therapies for management of ALS as of May 2017 with the approval of Radicava (edaravone):

3) **Riluzole (Rilutek)** was the first drug to receive FDA approval for ALS (December 1995). Riluzole is an oral formulation that acts to slow the progression of ALS symptoms and prolong survival. The exact mechanism in treating ALS is unknown; however, it is believed to block the release of glutamate from nerve cells thereby reducing the rate of glutamate-induced deterioration in nerve cells resulting in the slowing of initial progression of symptoms.
    - **Riluzole has demonstrated a slight increase overall survival (by 2-3 months), however it has not been shown to have an effect on physical functioning (has not been shown to modulate motor or respiratory function).** Clinical studies concluded that Rilutek may increase early survival by two to three months, but it does not improve muscle strength and neurological function, and has no effect in later stages of ALS.
    - Compared with placebo, riluzole may prolong median tracheostomy-free survival by 2-3 months in patients younger than 75 years with definite or probable ALS who have had the disease for less than 5 years and who have a forced vital capacity (FVC) of greater than 60%.

APPENDIX:
Diagnostic criteria
The El Escorial criteria were developed in 1994 by the World Federation of Neurology for research and clinical trial purposes. These guidelines were subsequently revised in recognition of the importance of laboratory testing, and were renamed the Airlie House criteria in 1998. The role of neurophysiology in diagnostic categorization has been further revised, and a subsidiary set of indicators—the Awaji–Shima criteria—was introduced in 2008, use of which improved diagnostic sensitivity without increasing false-positive rates

Revised El Escorial criteria: World Federation of Neurology consensus diagnostic criteria
The El Escorial Criteria (EEC) were developed in 1990 by the World Federation of Neurology and revised in 2000 to standardize the diagnosis of ALS for clinical research studies.

Currently, the ALS diagnostic criteria with the broadest international acceptance are the El Escorial revised Airlie House diagnostic criteria (Motor Neuron Diseases Research Group of the World Federation of Neurology) that were proposed in 1998. These criteria allow assignment of diagnostic certainty and were designed for research purposes to ensure appropriate inclusion of patients into clinical trials.

The El Escorial revised Airlie House diagnostic criteria grades the certainty of the diagnosis based upon 4 clinical grades:

- Clinically “Definite ALS” is defined on clinical evidence alone by the presence of upper motor neuron (UMN), as well as lower motor neuron (LMN) signs, in the bulbar region and at least 2 spinal regions or the presence of UMN and LMN signs in 3 spinal regions.
- Clinically “Probable ALS” is defined on clinical evidence alone by UMN and LMN signs in at least 2 regions with some UMN signs necessarily rostral to (above) the LMN signs.
- Clinically “Probable ALS Laboratory supported” is defined when clinical signs of UMN and LMN dysfunction are in only 1 region, or when UMN signs alone are present in 1 region, and LMN signs defined by electromyography criteria are present in at least 2 regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.
- Clinically “Possible ALS” is defined when clinical signs of UMN and LMN dysfunction are found together in only 1 region or UMN signs are found alone in 2 or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of Clinically Probable ALS Laboratory supported cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiologic, neuroimaging, or clinical laboratory studies. Other diagnoses must have been excluded to accept a diagnosis of Clinically Possible ALS.

Note: “Suspected ALS” is deleted from the revised El Escorial Criteria

By the revised El Escorial criteria, diagnosis of ALS requires:

- Presence of :
  - evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiologic, or neuropathologic exam
  - evidence of upper motor neuron (UMN) degeneration by clinical exam
  - progressive spread of symptoms or signs within a region or to other regions, determined by history or exam
- Absence of:
  - electrophysiologic or pathologic evidence of other disease processes that might explain signs of LMN and/or UMN degeneration
  - neuroimaging evidence of other disease processes that might explain observed clinical and electrophysiologic signs
  -

ALS FUNCTIONAL RATING SCALE-REVISED (ALSFRS-R)

ALSFRS-R has been the most widely used composite measure of function in ALS over the last 15 years (Cedarbaum 1999) The ALSFRS-R scale consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients 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 to 4, with higher scores representing greater functional ability.
The ALSFRS-R includes 12 items measuring multiple aspects of daily functioning.

REFERENCES:

1. Rilutek (riluzole) [prescribing information]. Zug, Switzerland: Covis Pharmaceuticals, Inc; July 2016.
2. Miller RG, Jackson CE, Kasarkis EJ, et al. Practice parameter update: the care of the patient with amyotropic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review). Neurology 2009;73:1218-1226
3. Quality Standards Subcommittee of the American Academy of Neurology. Practice advisory on the treatment of amytrophic lateral sclerosis with riluzole: a report of the quality standards subcommittee of the American Academy of Neurology. Neurology 1997;49:657-659
4. Bensimon G, Lacomblez L, Meininger et al. A controlled trial of riluzole in amyotrophic lateral sclerosis. N Engl J Med 1994;330:585-91
5. Tiglutik (riluzole) [prescribing information]. Berwyn, PA: ITF Pharma Inc; September 2018.