Original Effective Date: 08/30/2023
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Last P&T Approval/Version: 04/24/2024
Next Review Due By: 04/2025
Policy Number: C25487-A

Qalsody (tofersen)

PRODUCTS AFFECTED

Qalsody (tofersen)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This 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 Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Amyotrophic lateral sclerosis (ALS)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. AMYOTROPHIC LATERAL SCLEROSIS (ALS):
   1. Documentation of diagnosis of amyotrophic lateral sclerosis (ALS)
      AND
   2. Documentation of mutation in the superoxide dismutase 1 (SOD1) gene [DOCUMENTATION

REQUIRED]
[REVIEWER NOTE: Biogen offers no-charge genetic testing in the US https://www.invitae.com/en/sponsored-testing/als-identified]
AND

3. Documentation of a forced vital capacity (FVC) ≥50% of predicted value as adjusted for sex, age, and height (from the sitting position).

CONTINUATION OF THERAPY:

A. AMYOTROPHIC LATERAL SCLEROSIS (ALS):

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
3. Documentation member is not dependent on invasive ventilation or tracheostomy [DOCUMENTATION REQUIRED]

DURATION OF APPROVAL:
Initial authorization: 6 months, Continuation of Therapy: 6 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified neurologist, neuromuscular specialist, or physician experienced in the management/treatment of amyotrophic lateral sclerosis (ALS) [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
Loading dose: Three (3) 100 mg doses administered every 14 days; Maintenance dose: 100 mg every 28 days, following 3rd loading dose.

PLACE OF ADMINISTRATION:
The recommendation is that intrathecally infused medications in this policy will be for medical benefit coverage administered in a place of service that is a non-inpatient hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intrathecal

DRUG CLASS:
ALS Agents - Antisense Oligonucleotides

FDA-APPROVED USES:
Indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene.

This indication is approved under accelerated approval based on reduction in plasma neurofilament light chain observed in patients treated with QALSODY. Continued approval for this indication may be contingent

upon verification of clinical benefit in confirmatory trial(s).

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Amyotrophic Lateral Sclerosis (ALS), which is also known as Charcot's disease and Lou Gehrig's disease, is characterized by slowly progressive degeneration of upper motor neurons (UMNs) and lower motor neurons (LMNs). ALS is 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. The cause of the disease is unknown, and there is no cure. ALS is one of the most common neuromuscular diseases 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. ALS most commonly affects individuals 40-60 years old, but younger and older people can also 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 is primarily managed with symptomatic treatment and palliative care. There is no known cure for ALS at the present time. There are currently three FDA approved therapies for management of ALS as of May 2023 with the approval of Relyvrio (Sodium phenylbutyrate; taurursodiol).

riluzole (Rilutek)
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. Its 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 riluzole 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%.

Radicava (edaravone)
Radicava (edaravone) received FDA approval on May 5, 2017 for the treatment of patients with ALS. Radicava was the second drug to be approved for treatment of ALS, more than two decades from the first FDA approval of riluzole. Edaravone is a pyrazolone free radical scavenger. The mechanism by which the drug exerts its therapeutic effects in ALS in unknown. It is theorized to decrease effects of oxidative stress, a likely factor in the onset and progression of ALS. Administration is by IV infusion, requiring it to begiven by a healthcare professional and monitoring for infusion-related reactions.

Relyvrio (sodium phenylbutyrate/taurursodiol)

Relyvrio (sodium phenylbutyrate/taurursodiol) is an oral, fixed-dose combination therapy that is thought to target endoplasmic reticulum stress and mitochondrial dysfunction for the treatment of ALS. The FDA approval was supported by data from the phase 2 CENTAUR trial, a double-blind, placebo-controlled, parallel-group study that evaluated Relyvrio in adult patients with ALS (N=137) and the CENTAUR open-label extension (OLE) study. Patients were randomly assigned to receive Relyvrio (n=89) or placebo (n=48) for 24 weeks (intent-to-treat [ITT] population); baseline disease characteristics were reported to be comparable between the 2 groups. The primary endpoint of the study was a comparison of the rate of reduction in the ALS Functional Rating Scale-Revised (ALSFRS-R) total scores from baseline to week 24 in the mITT population. Results showed a statistically significant difference in the rate of reduction in the ALSFRS-R total score from baseline to week 24 in the Relyvrio group compared with the placebo group (treatment difference, 2.32 points [95% CI, 0.18-4.47]; P =.034).

The CENTAUR-OLE trial was a single-arm, open-label extension study in which participants completing the 6-month randomized phase (the CENTAUR trial) were eligible to receive Relyvrio for up to 30 months (132 weeks). Overall, 66% of participants originally randomized in the CENTAUR trial enrolled in the OLE, which included 56 participants (64%) from the Relyvrio arm and 34 participants (71%) from the placebo arm. The post-hoc, long-term, intention-to-treat (ITT) survival analysis showed a difference in median survival of 4.8 months in the group originally randomized to

Relyvrio compared to those originally randomized to placebo (23.5 months and 18.7 months, respectively; HR, 0.64; 95% CI, 0.42–0.995, P = 0.0475).

Qalsody (tofersen)

Efficacy: The clinical trial that led to FDA approval was the VALOR (NCT02623699) study, which was a 28-week, Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability, pharmacodynamic, and biomarker effects of Qalsody 100 mg in adults with superoxide dismutase 1 ALS (SOD1-ALS). The trial included a 4-week screening period, a 24-week treatment period, and a follow-up period of 4–8 weeks followed by an ongoing open-label extension (OLE) phase. The study population consisted of patients 23–78 years of age (average age: 49.8 years) with weakness attributable to SOD1-ALS confirmed by a central laboratory. The population was 43% female and 57% male with a mean baseline ALSFRS-R score of 36.9 (5.9) in the Qalsody treatment group and 37.3 (5.8) in the placebo group. The median time from symptom onset was 11.4 months in the Qalsody treatment group and 14.6 months in the placebo group. 108 patients were randomized 2:1 to receive 8 doses (3 loading doses followed by 5 maintenance doses) of one of the following for 24 weeks: Qalsody 100 mg (n = 72) or Placebo (n = 36). At baseline, 62% of patients were taking riluzole and 8% of patients were taking edaravone. The primary endpoints were change from baseline to Week 28 in ALSFRS-R total score in the modified intention-to-treat (mITT) population and secondary endpoints evaluated changes in total concentration of SOD1 protein in CSF, in the concentration of neurofilament light chains in plasma, in SVC, and in handheld dynamometry megascore in 16 muscle group, time to death or permanent ventilation, the time to death, and safety.

Among the modifed intent-to-treat (mITT) population, the change in the ALS Functional Rating Scale–Revised (ALSFRS-R) total score from baseline to Week 28 was –6.98 points in the Qalsody group and –8.14 in the placebo group, which was not statistically significant (difference, 1.2 points; 95% confidence interval [CI], –3.2 to 5.5; P = 0.97). In addition, none of the clinical secondary outcomes were statistically significant. However, secondary endpoints of change from baseline at

Week 28 in plasma neurofilament light chain (NfL) and cerebrospinal fluid (CSF) SOD1 protein were nominally statistically significant.

Safety: Neurologic serious adverse events, which included myelitis, chemical or aseptic meningitis, lumbar radiculopathy, increased intracranial pressure, and papilledema, occurred in 7% of participants receiving Qalsody (4 participants in VALOR and 3 in the OLE). The most common side effects in the clinical trial (≥10% of patients treated with Qalsody and greater than placebo) included pain, fatigue, arthralgia, CSF white blood cell increased, and myalgia.

Qalsody was approved under the accelerated approval pathway, which allows the FDA to approve drugs for serious conditions with an unmet medical need when a drug has been shown to have an effect on a

surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. The approval of Qalsody was based on a reduction in plasma neurofilament light chain (NfL), a biomarker of axonal injury and neurodegeneration.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Qalsody (tofersen) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Qalsody (tofersen) include: no FDA labeled contraindications currently.

OTHER SPECIAL CONSIDERATIONS:
Qalsody (tofersen) is administered intrathecally.
Preparation and Administration Instructions
• Allow to warm to room temperature prior to administration
• Administer within 4 hours of removal from vial
• Prior to administration, remove approximately 10 mL of cerebrospinal fluid
• Administer as an intrathecal bolus injection over 1 to 3 minute

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J1304	Injection, tofersen, 1 mg

AVAILABLE DOSAGE FORMS:
Qalsody SOLN 100 mg/15 mL single-dose vial

REFERENCES

1. Qalsody (tofersen) [prescribing information]. Cambridge, MA: Biogen MA Inc; April 2023.
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3. Miller T, et al. Phase 1–2 trial of antisense oligonucleotide tofersen for SOD1 ALS. N Engl J Med. 2020;383(2):109–119. doi:10.1056/NEJMoa2003715
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5. Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16(7):505–512. doi:10.1016/S1474- 4422(17)30115-1
6. Paganoni S, et al. Effect of sodium phenylbutyrate/taurursodiol on tracheostomy/ventilation-free survival and hospitalization in amyotrophic lateral sclerosis: long-term results from the CENTAUR trial [published online ahead of print, May 16, 2022].
7. Miller RG, Jackson CE, Kasarkis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence- based review).

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements	Q2 2024
NEW CRITERIA	Q3 2023