Effective Date **11/15/2023**
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Coverage Policy Number **IP0567**

Tofersen

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for tofersen intrathecal injection (**Qalsody**™).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Tofersen (Qalsody) is considered medically necessary when the following are met:

Amyotrophic Lateral Sclerosis (ALS). Individual meets **ALL** of the following criteria:
- A. Age 18 years or older
- B. Has weakness associated with ALS
- C. Documentation of **ONE** of the following:
  - i. Individual meets **BOTH** of the following:

a. Has **ONE** of the following pathogenic or likely pathogenic variants of the superoxide dismutase 1 (*SOD1*) gene: p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, or p.Val149Gly
b. Has a baseline Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R) slope decline of greater than or equal to 0.2 per month. (ALSFRS-R slope decline is calculated as [48 minus baseline ALSFRS-R total score/time since symptom onset])

ii. Individual meets **BOTH** of the following:
a. Has a *SOD1* genetic variant which is not listed here: p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, or p.Val149Gly
b. Has a baseline ALSFRS-R slope decline of greater than or equal to 0.9 per month (ALSFRS-R slope decline is calculated as [48 minus baseline ALSFRS-R total score/time since symptom onset])

D. Documentation of elevated plasma (serum) neurofilament light chain levels at baseline
E. Documentation of a slow vital capacity (SVC) of greater than or equal to 65% of predicted value for sex, age, and height (from the sitting position)
F. Has received or is currently receiving riluzole tablets, Tiglutik (riluzole oral suspension), or Exservan (riluzole oral film)
G. Medication is prescribed by, or in consultation with, a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS

Dosing. Three initial loading doses of 100 mg (15 mL), each given every 14 days administered intrathecally, followed by a maintenance dose of 100 mg (15 mL) administered intrathecally not more frequently than once every 28 days

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When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of tofersen (Qalsody) is considered medically necessary for the treatment of amyotrophic lateral sclerosis (ALS) when the individual meets **ALL** of the following:

1. Age 18 years or older
2. Has weakness associated with ALS
3. Has a superoxide dismutase 1 (*SOD1*) genetic variant
4. Does not require invasive ventilation
5. Individual continues to benefit from therapy
6. Medication is prescribed by, or in consultation with, a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS

Authorization Duration

Initial approval duration: up to 6 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven.

Coding Information

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.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J1304	Injection, tofersen, 1 mg

Background

OVERVIEW

Qalsody, an antisense oligonucleotide, is indicated for the treatment of **amyotrophic lateral sclerosis (ALS)** in adults who have a **mutation** in the **superoxide dismutase 1 (*SOD1*) gene**.[1]

Clinical Efficacy

The efficacy of Qalsody was evaluated in one Phase III, randomized, double-blind, placebo-controlled, multicenter, pivotal study (VALOR) in patients with SOD1-ALS (published) [n=108].[2] Patients were divided into the faster-progression subgroup or slower-progression subgroup based on trial-defined prognostic criteria. The primary analysis population was the faster-progression subgroup (n = 60) in which the primary and key secondary endpoints were formally tested. The faster-progression subgroup were required to have slow vital capacity (SVC) ≥ 65% of predicted value for sex, age, and height (from the sitting position) at screening and meet the following criteria: one of the following pathogenic or likely pathogenic *SOD1* mutations (i.e., p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, or p.Val149Gly), and a pre-study Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) slope decline ≥ 0.2 points per month (calculated as [48 minus baseline ALSFRS-R total score]/time since symptom onset); OR a *SOD1* mutation other than those listed above and prerandomization ALSFRS-R slope decline ≥ 0.9 points per month. The slower-progression subgroup (n = 48) had a non-protocol-defined pathogenic or likely pathogenic *SOD1* mutation type and pre-study ALSFRS-R slope decline of < 0.9 points per month, and had an SVC ≥ 50% of predicted value as adjusted for sex, age, and height (from the sitting position) at screening. The slower-progression subgroup were not included in the primary endpoint analysis, but were allowed to enroll in the open-label extension to receive Qalsody. Formal testing for statistical significance was only prespecified for total CSF SOD1 protein in the slower-progression subgroup.

The randomized portion of the trial was 28 weeks followed by an ongoing open-label extension phase.[2] A combined analysis of the randomized component of the trial and its open-label extension at 52 weeks compared the results in patients who started Qalsody at trial entry (early-start cohort) with those who switched from placebo to Qalsody at Week 28 (delayed-start cohort). At baseline, 62% and 8% of patients were taking riluzole and Radicava® (edaravone intravenous infusion and oral suspension), respectively, for ALS. In the randomized component of VALOR, in the faster-progression subgroup, no significant difference was observed between Qalsody and placebo in the primary endpoint, which was the change from baseline to Week 28 in the ALSFRS-R score; the change in the ALSFRS-R score was -6.98 points in the Qalsody group and -8.14 points in the placebo group with a difference of 1.2 points (95% confidence interval [CI]: -3.2, 5.5; P = 0.97). Qalsody led to greater reduction of mean concentration of plasma neurofilament light chains compared with placebo. The mean concentration of neurofilament light chains in plasma was reduced by 60% in the Qalsody group and increased by 20% in the placebo group and Qalsody led to a greater reduction in the total concentration of SOD1 protein in cerebrospinal fluid compared with placebo. The total concentration of SOD1 protein in CSF was decreased by 29% in the Qalsody group vs. an increase of 16% in the placebo group. In the overall population (which included the faster and slower progression subgroups), the mean plasma concentration of neurofilament light chains was reduced by 55% in the Qalsody group vs. a 12% increase in placebo group. The total concentration of SOD1 protein in CSF was reduced by 35% in the Qalsody group vs. 2% in the placebo group. Median time to death or permanent ventilation could not be estimated. Results of other secondary endpoints did not differ between the two groups.

Guidelines
The American Academy of Neurology (AAN) practice parameter on the care of patients with ALS (last updated 2009; reaffirmed 2023) does not address Qalsody, Relyvrio, Radicava ORS, or Radicava IV.[3,4] The practice parameter states that riluzole is safe and effective for slowing disease progression to a modest degree and should be offered to patients with ALS. However, riluzole may result in fatigue in some patients and if the risk of fatigue outweighs modest survival benefits, discontinuation of riluzole may be considered. Referral to a specialized multidisciplinary clinic should be considered for patients with ALS to optimize health care delivery, prolong survival, and enhance quality of life.

The European Federation of Neurological Societies (EFNS) guidelines on the clinical management of ALS (2012) also recommend patients be offered treatment with riluzole as early as possible after diagnosis.[5] Qalsody is not mentioned in these guidelines. New guidelines on the management of ALS were presented at the European Academy of Neurology 2023 meeting and are expected to be published before the end of 2023.[6] The recommendations during this meeting stated that Qalsody should be offered as first-line treatment in patients with progressive ALS caused by mutations in *SOD1*.[6]

The Canadian best practice recommendations for the management of ALS state that riluzole has demonstrated efficacy in improving survival in ALS and there is evidence that riluzole prolongs survival by a median duration of 3 months.[7] Riluzole should be started soon after the diagnosis of ALS. In a select group of patients, Radicava has been shown to slow decline on the ALSFRS-R scores compared against intravenous (IV) placebo over a 6-month period. The following patients have demonstrated a benefit of Radicava: patients with a disease duration < 2 years, forced vital capacity > 80%, all ALSFRS-R subcomponent scores > 2, and patients who have demonstrated steady decline in the ALSFRS-R over a 3-month period. Evidence for benefit of Radicava IV at other stages of ALS have not been demonstrated. Risks and benefits as well as individualized goals should be considered and discussed before starting therapy with Radicava IV. Qalsody is not mentioned in these guidelines.

Dosing Information
Qalsody should be initiated with three loading doses administered at 14-day intervals.[1] The recommended dose of Qalsody is 100 mg (15 mL) administered intrathecally using a lumbar puncture, by, or under direction or, healthcare professionals experience in performing lumbar punctures. The maintenance dose of Qalsody is 100 mg every 28 days.

References

1. Qalsody™ intrathecal injection [prescribing information]. Cambridge, MA: Biogen; April 2023.
2. Miller TM, Cudkowicz ME, Genge A, et al. Trial of antisense oligonucleotide tofersen for *SOD1* ALS. *N Engl J Med*. 2022;387:1099-110.
3. 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 2023);73(15):1227-1233.
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;73:1218-1226.
5. Andersen PM, Abrahams S, Borasio GD, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS) – revised report of an EFNS task force. *Eur J Neurol*. 2012;19(3):360-375.
6. New EAN Guidelines on ALS Management. Physician's Weekly. July 10, 2023. Available at: https://www.physiciansweekly.com/new-ean-guidelines-on-als-management/. Accessed on August 3, 2023.
7. Shoesmith C, Abrahao A, Benstead T, et al. Canadian best practice recommendations for the management of amyotrophic lateral sclerosis. *CMAJ*. 2020;192(46):E1453-E1468.