09-J4000-59

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Reviewed: 08/14/24

Revised: 09/15/24

Subject: Tofersen (Qalsody) for Intrathecal Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Amyotrophic lateral sclerosis (ALS) is a debilitating disease caused by degeneration of cortical, brainstem, and spinal cord motor neurons and, in some cases, frontotemporal cortical neurons. The neurodegeneration results in progressive muscle weakness, muscle spasticity, dysarthria, dysphagia, cognitive and behavioral impairments, and other motor symptoms. The exact etiology of ALS is unclear but is likely due to multiple genetic (e.g., C9orf72, TARDBP, SOD1, FUS genes) and environmental factors. The superoxide dismutase 1 (SOD1) gene mutation affects approximately 2% of ALS cases, which equates to about 500 patients in the United States. Onset typically occurs at age 50 to 75 years and is more frequently reported in males than females, with a lifetime risk of about 0.29% and 0.25%, respectively. Unfortunately, prognosis is poor with a median survival of 2 to 4 years, and respiratory insufficiency is the most common cause of death.

Patients presenting with suspected ALS are typically evaluated using the revised El Escorial/Arlie House criteria, which utilize clinical and electrophysiologic evaluations to ensure all the hallmark signs and symptoms are present while ruling out other neurodegenerative diseases. Once diagnosed, therapeutic options include riluzole (Rilutek tablets, Tiglutik suspension, and Exservan oral film) 50 mg orally twice daily, which modulates the actions of glutamate to slow disease progression, edaravone (Radicava oral suspension), a free radical scavenger and antioxidant, as concomitant therapy or as monotherapy if the patient is intolerant to riluzole, and sodium phenylbutyrate-taurursodiol (Relyvrio) as monotherapy or in combination with any of the aforementioned agents. On April 25, 2023, the FDA granted accelerated approval for tofersen (Qalsody) for adult patients with ALS who have a mutation in the SOD1 gene, as the agent is an antisense oligonucleotide that targets SOD1 mRNA to reduce the synthesis of SOD1 protein. Continued approval is contingent upon verification of clinical benefit in confirmatory trial(s).

The efficacy of tofersen (Qalsody) was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (VALOR study). A total of 108 adult patients with SOD1 ALS were assigned 2:1 to receive

either eight doses of tofersen 100 mg (3 loading doses at 14-day intervals followed by 5 maintenance doses at 28-day intervals) or placebo as an intrathecal bolus injection over a period of 24 weeks. Concomitant use of riluzole and edaravone was permitted. The primary end point was the change from baseline to week 28 in the total score on the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R; total scores are zero to 48 with higher scores indicating better function; see Definitions) among participants predicted to have faster-progressing disease. Secondary end points included changes in the total concentration of SOD1 protein in cerebrospinal fluid (CSF), in the concentration of neurofilament light chains in plasma, in slow vital capacity, and in handheld dynamometry in 16 muscles. A total of 72 participants received tofersen (39 predicted to have faster progression), and 36 received placebo (21 predicted to have faster progression). In the faster-progression subgroup, the change at week 28 in the ALSFRS-R score was −6.98 with tofersen and −8.14 with placebo (difference, 1.2 points; 95% confidence interval, −3.2 to 5.5; P=0.97). Tofersen demonstrated a reduction in concentrations of SOD1 in CSF (35% reduction for tofersen compared to 2% for placebo; P=<0.0001) and neurofilament light chains in plasma (55% reduction for tofersen compared to a 12% increase for placebo; P=<0.0001). Results for other secondary end points did not differ significantly between the two groups.

Tofersen was further evaluated in an open-label extension phase. A total of 95 participants (88%) from the VALOR study entered the open-label tofersen extension; this population included patients that receive active drug therapy from the trial start (early-start) and those that switched from placebo to active drug at 28 weeks (delayed-start). At 52 weeks, the change in the ALSFRS-R score was −6.0 in the early-start cohort and −9.5 in the delayed-start cohort (difference, 3.5 points; 95% confidence interval, 0.4 to 6.7). The extension phase is ongoing, and final analysis scheduled to occur once participants have completed at least 3.5 years of follow-up.

The most frequently reported adverse events were consistent with ALS disease progression or side effects of lumbar puncture and included procedural pain, headache, pain in the arms or legs, falls, and back pain. Four patients in the VALOR study and three patients in the open-label extension who received tofersen had a total of eight neurologic serious adverse events (e.g., myelitis, chemical/aseptic meningitis, lumbar radiculopathy, increased intracranial pressure, papilledema).

POSITION STATEMENT:

Initiation of tofersen (Qalsody) **meets the definition of medical necessity** when **ALL** of the following are met:

1. Member has a diagnosis of amyotrophic lateral sclerosis (ALS) by a neurologist or neuromuscular specialist that meets either of the following categories of clinical diagnostic certainty (defined by the revised El Escorial/Arlie House criteria) – documentation from the medical record and all relevant diagnostic testing (e.g., imaging, nerve conduction studies) must be provided:
    a. Clinically Definite ALS
        i. Presence of upper motor neuron (UMN), as well as lower motor neuron (LMN) signs, in the bulbar region and at least two spinal regions OR the presence of UMN and LMN signs in three spinal regions
    b. Clinically Probable ALS

   i. Presence of UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs

2. Confirmed mutation in the superoxide dismutase 1 (SOD1) gene - documentation from the laboratory genetic test must be provided
3. Elevated plasma (serum) neurofilament light chain (NfL) at baseline - documentation from the medical record or lab results must be provided
4. Member does not require invasive ventilation measures such as mechanical ventilation by intubation or tracheostomy. Minimal ventilation measures such as oxygen via nasal cannula or BiPAP are permitted.
5. The medication is prescribed by, or in consultation with, a neurologist or neuromuscular specialist.
6. The dose does not exceed 100 mg intrathecally every 14 days for 3 doses, followed by 100 mg intrathecally every 28 days.

Approval duration: 6 months

Continuation of tofersen (Qalsody) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 90 days before the authorization request must be submitted), OR the member has previously met all indication-specific initiation criteria.
2. The member's plasma (serum) neurofilament light chain (NfL) has decreased from or remained below their pre-treatment NfL value - documentation from the medical record or lab results must be provided
3. Provider attestation that the patient has slowed disease progression from baseline.
4. The medication is prescribed by, or in consultation with, a neurologist or neuromuscular specialist.
5. The dose does not exceed 100 mg intrathecally every 14 days for 3 doses, followed by 100 mg intrathecally every 28 days.

Approval duration: 1 year

Tofersen (Qalsody) intrathecal injection is considered **experimental or investigational** for any other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcome.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Tofersen (Qalsody) is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene.
- The recommended dosage is 100 mg intrathecally every 14 days for 3 doses, followed by 100 mg intrathecally every 28 days.
- Allow tofersen (Qalsody) to warm to room temperature prior to administration.
- Administration should occur within 4 hours after removal from the vial.
- Prior to administration, approximately 10 mL of cerebrospinal fluid should be removed from the patient.
- Administration of the intrathecal tofersen bolus injection should occur over 1 to 3 minutes.

Dose Adjustments

- The effect of renal or hepatic impairment on the pharmacokinetics of tofersen (Qalsody) is unknown.

Drug Availability

- Tofersen (Qalsody) for intrathecal injection is a sterile, clear, and colorless to slightly yellow solution supplied as 100 mg/15 mL (6.7 mg/mL) solution in a single-dose glass vial free of preservatives (NDC 64406-109-01)

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Myelitis and/ or Radiculitis:** Serious events of myelitis and radiculitis have been reported. Monitor for symptoms; diagnostic workup and treatment should be initiated according to the standard of care.
- **Papilledema and Elevated Intracranial Pressure:** Serious events of papilledema and elevated intracranial pressure have been reported. Monitor for symptoms; diagnostic workup and treatment should be initiated according to standard of care.
- **Aseptic Meningitis:** Serious events of aseptic meningitis have been reported. Monitor for symptoms; diagnostic workup and treatment should be initiated according to standard of care.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J1304	Injection, tofersen, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

G12.21	Amyotrophic Lateral Sclerosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R): Standardized rubric used to stratify the severity of ALS. The rubric includes assessments of speech, salivation, swallowing, handwriting, evaluation of >50% daily nutrition intake via G-tube, cutting food and handling of utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency. Points are applied in each category from zero (complete loss of function) to +4 (no loss of function). The nutritional intake via G-tube is a yes/no response. Possible total scores are zero to 48 with higher scores indicating better function.

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2024. URL www.clinicalpharmacology-ip.com Accessed 7/30/24.
2. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2024. URL http://www.dynamed.com. Accessed 7/30/24.
3. Micromedex Healthcare Series [Internet Database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Accessed 7/30/24.

4. Pa Miller TM, Cudkowicz ME, Genge A, et al. Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS. *N Engl J Med*. 2022;387(12):1099-1110. doi:10.1056/NEJMoa2204705
5. Qalsody (tofersen) [package insert]. Biogen, Inc., Cambridge (MA): April 2023.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 08/14/24.

GUIDELINE UPDATE INFORMATION:

09/15/23	New Medical Coverage Guideline – Tofersen (Qalsody) for the treatment of amyotrophic lateral sclerosis (ALS) who have a mutation in the superoxide dismutase 1 (SOD1) gene.
10/01/23	Revision: Added HCPCS code C9157.
01/01/24	Revision: Added HCPCS code J1304 and deleted codes C9157 and J3590.
09/15/24	Review and revision to guideline consisting of updating the position statement to allow prescribing of tofersen (Qalsody) by, or in consultation with, a neurologist or neuromuscular specialist but limiting diagnosis to a specialist, requiring laboratory documentation for the genetic test, and updating references.