Oscar Clinical Guideline: Qalsody (tofersen) (PG151, Ver. 4)

Qalsody (tofersen)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by motor neuron death, resulting in muscle weakness, paralysis, and eventual respiratory failure. Tofersen (Qalsody) is an antisense oligonucleotide therapy specifically designed for ALS caused by mutations in the superoxide dismutase 1 (SOD1) gene. It aims to slow disease progression by reducing toxic SOD1 protein production.

Tofersen received accelerated approval from the FDA based on its ability to reduce plasma neurofilament light chain (NfL), a biomarker of neurodegeneration. However, confirmatory trials, such as the ongoing ATLAS study, are required to establish its clinical benefit. The VALOR trial, a pivotal Phase III study, did not demonstrate statistically significant improvements in clinical outcomes, such as ALS Functional Rating Scale-Revised (ALSFRS-R) scores, in the primary or secondary endpoints. Exploratory analyses from the open-label extension study suggest potential trends toward improved outcomes with earlier treatment, but these findings are not conclusive.

- Common adverse events associated with tofersen include procedural pain, headache, and lumbar puncture-related complications. Serious adverse events, such as myelitis, radiculitis, papilledema, and aseptic meningitis, have also been reported.

While tofersen offers a novel approach by targeting the genetic cause of ALS in SOD1 mutation patients, its clinical efficacy and long-term safety remain uncertain. Further evidence is needed to determine its role in ALS treatment.

Definitions

"Adverse events (AEs)" are unfavorable signs, symptoms, or diseases that occur during the course of treatment with a medication or intervention.

"Amyotrophic lateral sclerosis (ALS)" is a progressive neurodegenerative disease characterized by the death of motor neurons in the brain and spinal cord, resulting in muscle weakness, loss of motor function, and eventual paralysis.

"Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R)" is a tool used to assess functional abilities in patients with ALS, measuring four domains: breathing, bulbar, gross motor, and fine motor. Higher scores indicate better function.

"Cerebrospinal fluid (CSF)" is the fluid that surrounds the brain and spinal cord, which can be used to measure biomarkers and assess disease progression in ALS.

"Confirmatory trials" refers to additional clinical trials conducted to validate or confirm the results of previous studies, typically designed to replicate findings and further establish the clinical benefit and safety profile of a treatment.

"Efficacy information" refers to data that demonstrates the effectiveness or therapeutic benefits of a medication or intervention in treating a specific condition.

"Long-term outcomes" refers to the effects, benefits, or adverse events observed over an extended period of time, usually beyond the duration of a clinical trial, providing insights into the sustained efficacy and safety of a treatment.

"Open-label extension study" is a continuation of a clinical trial where patients who completed the original trial are offered the study drug or treatment under open-label conditions.

"Robust evidence" means strong, reliable, and conclusive evidence derived from well-designed and well-conducted clinical studies, often including randomized controlled trials, systematic reviews, and meta-analyses.

"Secondary endpoints" refers to additional outcome measures in a clinical trial that are evaluated to provide supplementary information beyond the primary endpoint, assessing different aspects of treatment efficacy or safety.

"Statistically significant" is a term used to describe results that are unlikely to have occurred by chance and are considered meaningful from a statistical perspective.

Policy Statement on Qalsody (tofersen) Efficacy Information

The use of Qalsody (tofersen) is considered not medically necessary for the treatment of amyotrophic lateral sclerosis (ALS) due to SOD1 mutations or any other indication. While Qalsody has received FDA accelerated approval based on its ability to reduce plasma neurofilament light chain (NfL), a biomarker of neurodegeneration, the available clinical evidence does not demonstrate that it provides clinically meaningful benefits in terms of improving functional outcomes or slowing disease progression.

- The VALOR trial and its open-label extension study did not demonstrate statistically significant improvements in clinically meaningful outcomes, such as ALS Functional Rating Scale-Revised (ALSFRS-R) scores or other secondary endpoints. While reductions in biomarkers such as plasma NfL and cerebrospinal fluid (CSF) SOD1 protein were observed, these biomarkers have not been validated as surrogate endpoints for clinical benefit in ALS.
- Serious adverse events, including myelitis, radiculitis, papilledema, and aseptic meningitis, have been reported in clinical trials. These safety concerns, combined with the lack of clear clinical efficacy, raise questions about the overall risk-benefit profile of Qalsody.
- Qalsody received accelerated approval based on biomarker reductions, with continued approval contingent upon verification of clinical benefit in confirmatory trials. The ongoing ATLAS study and other trials are required to establish its clinical utility.

Clinical Indications

Medical Necessity Criteria for Clinical Review

Indication-Specific Criteria

Amyotrophic Lateral Sclerosis (ALS) with a Superoxide Dismutase 1 (SOD1) Mutation

Due to the uncertain clinical evidence, the Plan does not have standard medical necessity criteria for Qalsody (tofersen) at this time. Coverage for Qalsody (tofersen) for members with confirmed SOD1-mutated ALS will be determined on a case-by-case basis.

Experimental or Investigational / Not Medically Necessary

Qalsody (tofersen) for any indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven.The Plan has determined that the available evidence does not support the clinical efficacy, safety, or medical necessity of Qalsody at this time.

- The VALOR trial did not show statistically significant improvements in ALSFRS-R scores or other clinically meaningful outcomes compared to placebo.
- Biomarker reductions (e.g., plasma NfL and CSF SOD1 protein) observed in clinical trials have not been validated as surrogate endpoints for clinical benefit in ALS.
- Serious adverse events, including myelitis, radiculitis, papilledema, and aseptic meningitis, were reported in clinical trials. These events raise concerns about the safety of Qalsody, particularly in the absence of clear clinical efficacy.
- While exploratory analyses from the open-label extension study suggest potential trends toward improved outcomes with earlier treatment, these findings are not statistically significant and should be interpreted with caution due to the limitations of uncontrolled data.
- Long-term efficacy and safety data are still pending from ongoing trials, such as the ATLAS study.
- Qalsody was approved under the FDA's accelerated approval pathway based on biomarker reductions, with continued approval contingent upon confirmatory evidence of clinical benefit. To date, such evidence has not been established.
- See Appendix A for additional information.

The Plan will continue to monitor emerging evidence, including results from ongoing clinical trials, and will reassess its position as new data become available. Until then, alternative treatment options with established efficacy and safety profiles, such as riluzole and edaravone, should be considered in consultation with healthcare providers.

Applicable Billing Codes

Table 1	
Service(s) name	
CPT/HCPCS Codes considered NOT medically necessary:	
Code	*Description*
62322	Injection(s), of diagnostic or therapeutic substance(s) (eg, anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, including needle or catheter placement, interlaminar epidural or subarachnoid, lumbar or sacral (caudal); without imaging guidance
62323	Injection(s), of diagnostic or therapeutic substance(s) (eg, anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, including needle or catheter placement, interlaminar epidural or subarachnoid, lumbar or sacral (caudal); with imaging guidance (ie, fluoroscopy or CT)
J1304	Injection, tofersen, 1 mg

Table 2	
ICD-10 codes considered NOT medically necessary:	
Code	*Description*
G12.21	Amyotrophic lateral sclerosis
G12.23	Primary lateral sclerosis

References

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Appendix A

Qalsody (tofersen) for Amyotrophic Lateral Sclerosis (ALS) due to SOD1 Mutation

- A 2025 real-world study[14] suggests that Qalsody sustained declines in serum NfL and CSF phosphorylated neurofilament heavy chain (pNFH), disease stabilization as assessed by the ALSFRS-R total score, and improvement in functional independence measured by the functional independence measure (FIM) motor score. ALSFRS-R is a standard outcome measure rating instrument for monitoring the progression of disability in patients with ALS. While improvement in function was observed, this study was descriptive in nature and enrolled a small sample size of 7 patients. The expected ALSFRS-R used as a potential means of predicting how a patient would have done without Qalsody treatment is not an accepted measure thus using it to estimate disease progression is inexact. Additionally, the study was not powered or analyzed statistically;

therefore, the magnitude of benefit against placebo continues to be unknown. The study notes that preservation of function and disease stabilization did not change quality of life as assessed by the ALS Assessment Questionnaire 5-Item Form (ALSAQ-5). Due to these concerns, this study limits the generalizability of the findings and contributes to the low quality of this study.

- A 2025 systematic review and meta-analysis[5] suggests that Qalsody reduces SOD1 and NfL levels and slow disease progression in *SOD1 ALS*. This study consisted of 2 randomized controlled trials (RCTs) that were VALOR and a phase 1-2 dose study, 5 cohort studies, 1 case series, and 4 case reports. The small sample size (N < 199), majority of studies included were in Germany, use of biomarkers, limit of one phase 3 RCT which did not find statistical significance (i.e., VALOR), high volume of observational studies, lack of control groups contribute to the low quality of this review and limit the generalizability of the findings. Additionally, a pre-post meta-analysis of five of the studies compared the ALS progression rate before and after treatment with Qalsody using mean difference. A pre-post meta-analysis is not considered reliable due to the effect of confounding factors resulting in biased outcomes and should be avoided in meta-analyses.

Clinical Guideline Revision / History Information

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