Oscar Clinical Guideline: Qalsody (tofersen) (PG151, Ver. 2)

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 partiesw 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 and paralysis. Tofersen (Qalsody) is an antisense oligonucleotide therapy specifically designed for ALS caused by SOD1 gene mutations. It aims to slow disease progression by reducing toxic SOD1 protein production.

The VALOR trial, including its pivotal phase III study, evaluated the safety and efficacy of tofersen. Unfortunately, tofersen did not demonstrate a significant advantage over placebo in the primary endpoint of ALSFRS-R score change in the faster progressing subgroup. Secondary clinical endpoints also did not show significant differences between treatment groups.

Common adverse events associated with tofersen treatment include those related to lumbar puncture, procedural pain, headache, and falls. Long-term data from an ongoing open-label extension study will provide further insights.

Prior to tofersen, riluzole and edaravone were the approved treatments for ALS. Tofersen offers a novel approach by targeting the underlying genetic cause in SOD1 mutation patients.

Although tofersen received accelerated approval based on reduced plasma neurofilament light chain levels, confirmatory trials like the phase III ATLAS study are required to establish its clinical benefit. More evidence is needed to determine the efficacy and safety of tofersen 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

Based on the current limited efficacy information, the lack of statistically significant clinical benefits, safety concerns, and the absence of robust evidence supporting the medical necessity of Qalsody (tofersen), it is considered experimental, investigational, or unproven. The available clinical evidence suggests that while Qalsody (tofersen) has shown potential in reducing SOD1 concentrations in cerebrospinal fluid (CSF), it has not demonstrated a significant clinical benefit. The Phase III trial did not show a statistically significant difference in ALSFRS-R scores or other secondary endpoints between Qalsody (tofersen) and placebo. Therefore, further well-designed clinical trials are needed to determine the effectiveness, long-term outcomes, and safety profile of Qalsody in the treatment of ALS due to SOD1 mutation.

Qalsody (tofersen) has been evaluated for the treatment of amyotrophic lateral sclerosis (ALS) due to SOD1 mutation in several clinical trials, including the VALOR Trial, which comprised three parts: Phase I randomized single ascending dose study (part A), Phase I/II randomized multiple ascending dose study (part B), and Phase III pivotal randomized placebo-controlled fixed-dose study (part C). Additionally, a small first-in-human study was also conducted.

- In Phase I/II Part B of the VALOR Trial, the primary objective was to assess the safety, pharmacokinetics, and pharmacodynamics of tofersen in adults with ALS. The study included patients with documented SOD1 gene mutation and muscle weakness attributed to ALS. The trial randomized 50 adults to receive placebo or one of four tofersen doses. The study primarily evaluated adverse events (AEs), pharmacokinetics, and pharmacodynamics, while clinical efficacy

assessments were exploratory. Common AEs reported among tofersen-treated patients included headache, LP procedural pain, post-LP syndrome, and falls. Notably, serious adverse events (SAEs) were reported in some tofersen-treated patients, with the highest incidence observed in the lower-dose cohorts. Tofersen treatment at a dose of 100 mg resulted in a significant reduction of SOD1 concentrations in cerebrospinal fluid (CSF).

- Phase III Part C of the VALOR Trial aimed to evaluate the efficacy and safety of tofersen in adults with ALS due to SOD1 gene mutation. The trial included patients with muscle weakness attributed to ALS and a documented SOD1 gene mutation. Patients were randomized to receive intrathecal injections of either tofersen or placebo over 24 weeks. The primary efficacy endpoint was the change in ALS Functional Rating Scale–Revised (ALSFRS-R) from baseline to week 28 in the faster progressing subgroup. Secondary endpoints included changes in SOD1 protein concentrations in CSF, plasma neurofilament light chains, handheld dynamometry megascore, percentage of predicted slow vital capacity, and safety. The study did not demonstrate a statistically significant difference between tofersen and placebo in the primary or secondary clinical endpoints. The incidence of AEs and SAEs was relatively high in both treatment groups, with the most common AEs including events related to lumbar puncture, procedural pain, headache, and events related to the trial agent.

Medical Necessity Criteria for Qalsody (tofersen)

The available clinical evidence from the VALOR Trial evaluating Qalsody (tofersen) for the treatment of amyotrophic lateral sclerosis (ALS) due to SOD1 mutation indicates that the efficacy information is insufficient to determine if the medication exhibits any clinically meaningful benefits. The VALOR Trial consisted of a phase I/II study (part B) and a phase III study (part C), both of which explored the safety, pharmacokinetics, pharmacodynamics, and clinical efficacy of tofersen in ALS patients with SOD1 gene mutations.

In the phase I/II study, the primary objective was to assess the reduction of SOD1 protein concentrations in the cerebrospinal fluid (CSF). Although tofersen demonstrated a decrease in CSF SOD1 concentrations compared to placebo, this study was not powered to evaluate the clinical or biological measures of ALS beyond the biomarker reduction.

The phase III study aimed to evaluate the efficacy and safety of tofersen in ALS patients with SOD1 gene mutations. However, the primary efficacy endpoint, as measured by the change in the ALS Functional Rating Scale–Revised (ALSFRS-R) total score from baseline to week 28 in the faster progressing

subgroup, did not reach statistical significance. The majority of patients in both the tofersen and placebo groups experienced adverse events, with no statistically significant differences in secondary clinical endpoints observed.

Considering the limited evidence available, it is clear that there is insufficient information to establish medical necessity criteria for coverage of Qalsody. The efficacy results are inconclusive, and the clinical benefits of tofersen have not been adequately demonstrated. The safety profile also raises concerns, particularly regarding adverse events related to lumbar puncture. Therefore, the Plan does not recommend approval for the product at this time, and maintains that further well-designed clinical trials are warranted to support any future decision on its efficacy, safety, and clinical utility in ALS patients with SOD1 gene mutations.

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 thoroughly reviewed the available clinical evidence and has concluded that Qalsody (tofersen) is not considered medically necessary at this time due to the following reasons:

1. The available clinical trials evaluating Qalsody for the treatment of amyotrophic lateral sclerosis (ALS) due to SOD1 mutation have not demonstrated statistically significant improvements in clinically meaningful outcomes. The primary efficacy analysis, measuring change from baseline in the ALS Functional Rating Scale–Revised (ALSFRS-R) total score, did not show a significant difference between Qalsody and placebo. Secondary clinical endpoints also did not reach statistical significance. These findings indicate a lack of compelling evidence for the clinical efficacy of Qalsody in improving ALS-related functional decline.
2. The clinical trials have reported a range of adverse events associated with Qalsody treatment, including headache, procedural pain, post-lumbar puncture syndrome, falls, arm or leg pain, back pain, and ocular adverse events. Serious adverse events were reported in both the Qalsody and placebo groups. These safety concerns, coupled with the absence of clear clinical benefit, raise further doubts about the risk-benefit profile of Qalsody.
3. The available data on the long-term efficacy of Qalsody is limited. Although an open-label extension study is ongoing, comprehensive analyses of the long-term effects are pending, and it is unclear whether Qalsody can provide sustained benefits in preserving functional abilities or slowing disease progression over an extended period.

Based on the above considerations, the Plan has determined that Qalsody (tofersen) does not meet the criteria of medical necessity for the treatment of ALS due to SOD1 mutation at this time. The Plan is dedicated to providing coverage for treatments that have demonstrated both safety and effectiveness based on robust clinical evidence. Continued monitoring of the evolving clinical evidence for Qalsody will be conducted, and the Plan will reassess its position as more information becomes available. In the interim, alternative treatment options with established efficacy and safety profiles should be considered in consultation with healthcare providers.

Applicable Billing Codes (HCPCS/CPT Codes)

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)
C9157	Injection, tofersen, 1 mg
ICD-10 codes considered NOT medically necessary:	
Code	*Description*
G12.21	Amyotrophic lateral sclerosis
G12.23	Primary lateral sclerosis

References

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Clinical Guideline Revision / History Information

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