Policy Number	**RX501.162**
Policy Effective Date	**09/15/2024**
Policy End Date	**12/31/2025**

Tofersen

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and is not to be used for current claims adjudication or business purposes.

See RX501.087 FDA - Drugs, Biologicals, Cellular and Gene Therapies for dates of service 12/31/2025 and after.

Tofersen (Qalsody™) **is considered not medically necessary** for the treatment of amyotrophic lateral sclerosis (ALS), as a clinical benefit has not been established.

Tofersen (Qalsody™) **is considered experimental, investigational, and/or unproven** for all other indications.

Policy Guidelines

None.

Description

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's Disease, is a rare neurological disease that affects the nerve cells in the brain and spinal cord that control voluntary muscle movement (i.e., motor neurons). (1) As motor neurons degenerate and die, they stop sending messages to the muscles, which causes the muscles to weaken and atrophy. Eventually, the brain loses its ability to initiate and control voluntary movements.

There is no single test that can conclusively diagnose ALS. Along with a physical exam and full medical history, regular neurologic examinations to test reflexes, muscle strength, etc., are used to assess whether symptoms such as muscle weakness, muscle wasting, and spasticity are worsening. Muscle and imaging tests commonly performed to rule out other diseases and confirm the diagnosis include the following: electromyography (EMG), nerve condition studies (NCS), magnetic resonance imaging (MRI) of the brain and spinal cord, muscle biopsy, and laboratory testing. (1)

Although the vast majority of ALS cases occur randomly with no clearly associated risk factors, about 5 to 10% of all ALS cases are familial (i.e., inherited or genetic). Of those familial cases, 12

to 20% results from mutation in the superoxide dismutase 1 (SOD1) gene that is involved in the production of the enzyme copper-zinc superoxide dismutase 1. (1)

Although there is no cure, several medications have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of ALS, including riluzole (Rilutek), edaravone (Radicava), and most recently, tofersen (Qalsody™).

Qalsody (tofersen) is an antisense oligonucleotide that causes degradation of SOD1 messenger ribonucleic acid (mRNA) through binding to SOD1 mRNA, which results in a reduction of SOD1 protein synthesis. (2)

Regulatory Status
On April 25, 2023, the U.S. FDA approved tofersen (Qalsody™) (Biogen, Inc.) for the treatment of ALS in adults who have a mutation in the SOD1 gene. This indication was approved under accelerated approval based on reduction in plasma neurofilament light chain (NfL) observed in patients treated with Qalsody. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). (2)

Rationale

This medical policy was developed in July 2023 and is based on the clinical study provided to the U.S. Food and Drug Administration for accelerated approval.

Tofersen (Qalsody™) (2)
The efficacy of Qalsody was assessed in a 28-week randomized, double-blind, placebo-controlled clinical study in patients 23 to 78 years of age with weakness attributable to amyotrophic lateral sclerosis (ALS) and a superoxide dismutase 1 (SOD1) mutation confirmed by a central laboratory (Study 1 Part C, NCT02623699). One hundred eight (108) patients were randomized 2:1 to receive treatment with either Qalsody 100 mg (n = 72) or placebo (n = 36) for 24 weeks (3 loading doses followed by 5 maintenance doses). Concomitant riluzole and/or edaravone use was permitted for patients.

The prespecified primary analysis population (n = 60, modified intent to treat [mITT]) had a slow vital capacity (SVC) ≥ 65% of predicted value and met prognostic enrichment criteria for rapid disease progression, defined based on their pre-randomization ALS Functional Rating Scale–Revised (ALSFRS-R) decline slope and SOD1 mutation type.

The non-mITT population (n = 48) had a slow vital capacity (SVC) ≥ 50% of predicted value and did not meet the enrichment criteria for rapid disease progression. Baseline disease characteristics in the overall intent-to-treat (ITT) population (combined mITT and non-mITT population) were generally similar in patients treated with Qalsody and patients who received placebo, with slightly shorter time from symptom onset and higher plasma neurofilament light chain (NfL) at baseline in the Qalsody group. At baseline, 62% of patients were taking riluzole,

and 8% of patients were taking edaravone. Mean baseline ALSFRS-R score was 36.9 (5.9) in the Qalsody treatment group and 37.3 (5.8) in the placebo group. Median time from symptom onset was 11.4 months in the Qalsody treatment group and 14.6 months in the placebo group.

The primary efficacy analysis was the change from baseline to Week 28 in the ALSFRS-R total score in the mITT population, analyzed using the joint rank test to account for mortality in conjunction with multiple imputation (MI) to account for missing data for withdrawals other than death. Patients treated with Qalsody experienced less decline from baseline in the ALSFRS-R compared to placebo, but the results were not statistically significant (Qalsody-placebo adjusted mean difference [95% CI]: 1.2 [-3.2, 5.5]). Other clinical secondary outcomes also did not reach statistical significance.

Secondary endpoints of change from baseline at Week 28 in plasma NfL and cerebrospinal fluid (CSF) SOD1 protein were nominally statistically significant (see Table 1). NfL reduction was consistently observed for all subgroups based on sex, disease duration since symptom onset, site of onset, and riluzole/edaravone use.

Table 1: Biomarker Results of QALSODY in Study 1 Part C at Week 28

Biomarker Endpoints	Qalsody	Placebo
Plasma NfL		
ITT population	N=72	N=36
Adjusted geometric mean ratio to baseline	0.45	1.12
Qalsody to placebo difference in geometric mean ratio (95% CI) Nominal p-value (ANCOVA+MI)	0.40 (0.33, 0.49) <0.0001	
mITT population	N=39	N=21
Adjusted geometric mean ratio to baseline	0.40	1.20
Qalsody to placebo difference in geometric mean ratio (95% CI) Nominal p-value (ANCOVA+MI)	0.33 (0.25, 0.45) <0.0001	
CSF SOD1 Protein		
ITT population	N=72	N=36
Adjusted geometric mean ratio to baseline	0.65	0.98
Qalsody to placebo difference in geometric mean ratio (95% CI)	0.66 (0.57, 0.77)	

Nominal p-value (ANCOVA+MI)	<0.0001	
mITT population	N=39	N=21
Adjusted geometric mean ratio to baseline	0.71	1.16
Qalsody to placebo difference in geometric mean ratio (95% CI)	0.62 (0.49, 0.78)	
Nominal p-value (ANCOVA+MI)	<0.0001	

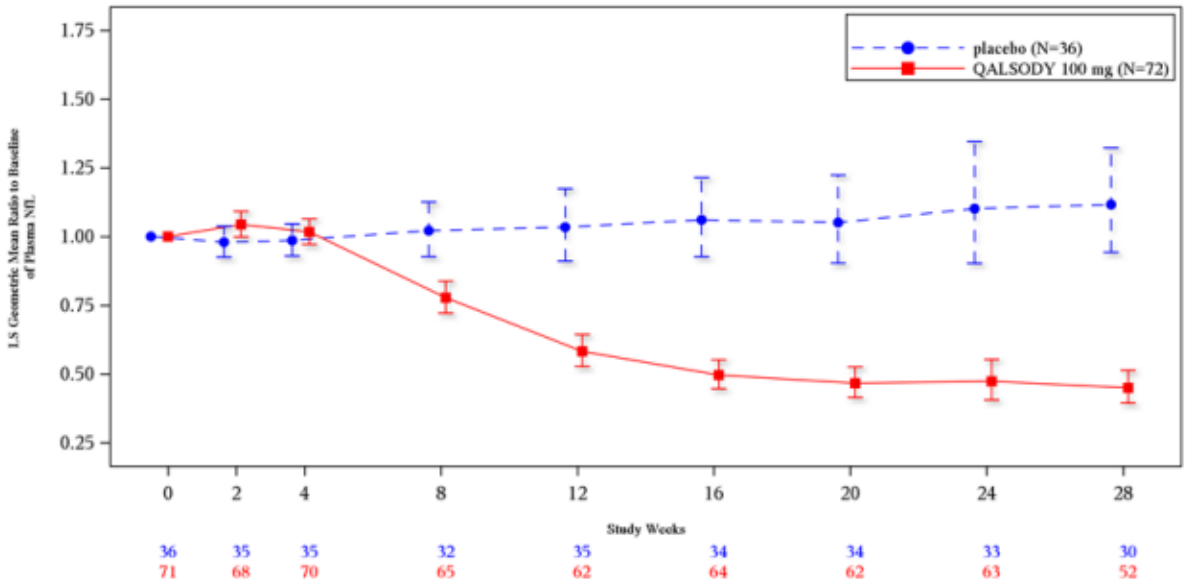
CI: confidence interval; ITT: intent-to-treat; mITT: modified intent-to-treat; MI: multiple imputation; NfL: neurofilament light chain.

Note 1: N is the number of patients with baseline value.

Note 2: MI was used for missing data. Model included treatment, use of riluzole or edaravone, relevant baseline score and postbaseline values (natural log transformed data). Separate models for mITT and non-mITT were used and combined for ITT analyses.

Note 3: Adjusted geometric mean ratios to baseline, treatment differences in adjusted geometric mean ratios to baseline and corresponding 95% CIs and nominal p-values were obtained from the ANCOVA model for change from baseline including treatment as a fixed effect and adjusting for the following covariates: baseline disease duration since symptom onset, relevant baseline score, and use of riluzole or edaravone. The analysis was based on natural log transformed data.

Figure 1: Plasma NfL Adjusted Geometric Mean Ratio to Baseline Values in Study 1 Part C by Study Week for the ITT Population



After completion of Study 1, patients had the option to enroll in an open-label extension study. At an interim analysis at 52 weeks, reductions in NfL were seen in patients previously receiving placebo who initiated Qalsody in the open-label extension study, similar to the reductions seen in patients treated with Qalsody in Study 1. Earlier initiation of Qalsody compared to

placebo/delayed initiation of Qalsody was associated with trends for reduction in decline on ALSFRS-R, SVC percent-predicted, and hand-held dynamometry (HHD) megascore that were not statistically significant. Through all open-label follow-up at the time of the interim analysis, earlier initiation of Qalsody was also associated with a trend towards reduction of the risk of death or permanent ventilation, although it was not statistically significant. These exploratory analyses should be interpreted with caution given the limitations of data collected outside of a controlled study, which may be subject to confounding.

Summary of Evidence

For individuals who have been diagnosed with amyotrophic lateral sclerosis (ALS), the evidence includes a randomized, double-blind, placebo-controlled clinical trial in which the primary endpoint was not met. Although there were signs of reduced disease progression across secondary and exploratory measures of biologic activity and clinical function, uncertainties regarding clinical benefit remain.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1304, [Deleted 1/2024: C9157]

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. National Institute of Neurological Disorders and Stroke. Amyotrophic Lateral Sclerosis (ALS). Mar 08, 2023. Available at: <https://www.ninds.nih.gov> (accessed July 14, 2023).
2. FDA. Highlights of Prescribing Information - Qalsody™ (Tofersen). Revised 4/2023. Available at: <https://www.fda.gov> (accessed July 14, 2023).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
12/31/2025	Document became inactive.
09/15/2024	Reviewed. No changes.
01/15/2024	New medical document. Tofersen (Qalsody™) is considered not medically necessary for the treatment of amyotrophic lateral sclerosis (ALS), as a clinical benefit has not been established. Tofersen (Qalsody™) is considered experimental, investigational, and/or unproven for all other indications.