Qalsody™ (Tofersen)

Policy Number: 2023D00123B
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Instructions for Use

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Coverage Rationale

See Benefit Considerations

Qalsody (tofersen) is proven and medically necessary for the treatment of amyotrophic lateral sclerosis (ALS) in patients who meet all of the following criteria:

- For **initial therapy**, **all** of the following:
  - Submission of medical records (e.g., chart notes, previous medical history, diagnostic testing including: imaging, nerve conduction studies, laboratory values) to support the diagnosis of ALS[7]; **and**
  - Submission of medical records confirming mutation in the superoxide dismutase 1 (SOD1) gene; **and**
  - Provider attestation that the patient's baseline functional ability has been documented prior to initiating treatment (e.g., speech, walking, climbing stairs, etc.); **and**
  - Patient is **not** dependent on invasive ventilation or tracheostomy; **and**
  - Qalsody is prescribed by, or in consultation with, a neurologist with expertise in the diagnosis of ALS; **and**
  - Qalsody dosing for ALS is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Initial authorization will be for no more than 6 months.
- For **continuation of therapy**, **all** of the following:
  - Diagnosis of ALS; **and**
  - Patient is currently receiving Qalsody therapy; **and**
  - Provider attestation that the patient has slowed disease progression from baseline; **and**
  - Patient is **not** dependent on invasive ventilation or tracheostomy; **and**
  - Qalsody is prescribed by, or in consultation with, a neurologist with expertise in the diagnosis of ALS; **and**
  - Qalsody dosing for ALS is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Authorization will be for no more than 6 months.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may

require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
C9157	Injection, tofersen, 1 mg
J3490	Unclassified drugs
J3590	Unclassified biologics

Diagnosis Code	Description
G12.21	Amyotrophic lateral sclerosis

Background

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a rapidly progressive, invariably fatal neurological disease that attacks neurons responsible for controlling voluntary muscles. The disease belongs to a group of disorders known as motor neuron diseases, which are characterized by the gradual degeneration and death of motor neurons. Eventually, all muscles under voluntary control are affected. Individuals lose their strength and the ability to move their arms, legs, and body. When muscles in the diaphragm and chest wall fail, individuals lose the ability to breathe without ventilatory support. Individuals with ALS usually survive for only 3 to 5 years from the onset of symptoms. However, about 10 percent of those with ALS survive for 10 or more years.[8]

ALS can be categorized as familial or sporadic disease, depending on whether the patient has a family history of the disease or not.[9] Familial ALS accounts for approximately 10% of cases, and among these, C9ORF72 and SOD1 are the two most common causative genes. SOD1 encodes for superoxide dismutase, a mutated protein which has been associated with the degeneration of motor neurons. SOD1-ALS is the second most common form of familial ALS. There are approximately 16,000 people living with ALS in the United States, with an estimated prevalence of 5 patients per 100,000 population, and with 5,000 new cases diagnosed each year. 5-10% of ALS cases are familial and associated with approximately 50 different genes and approximately 2% of ALS cases are associated with mutations in the SOD1 gene. Familial ALS generally has an earlier onset (by about 10 years) than sporadic ALS.

Qalsody (tofersen) is an antisense oligonucleotide that causes degradation of SOD1 mRNA through binding to SOD1 mRNA, which results in a reduction of SOD1 protein synthesis.[1]

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

The efficacy of tofersen 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 ALS and a SOD1 mutation confirmed by a central laboratory (Study 1 Part C, NCT02623699).[1,10] One hundred eight (108) patients were randomized 2:1 to receive treatment with either tofersen 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 tofersen and patients who received placebo, with slightly shorter time from symptom onset and higher plasma neurofilament (NfL) at baseline in the tofersen 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 tofersen treatment group and 37.3 (5.8) in the placebo group. Median time from symptom onset was 11.4 months in the tofersen 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 tofersen experienced less decline from baseline in the ALSFRS-R compared to placebo, but the results were not statistically significant (tofersen-placebo adjusted mean difference [95% CI]: 1.2 [-3.2, 5.5]). Specifically, in the faster-progression subgroup (primary analysis), the change to week 28 in the ALSFRS-R score was −6.98 with tofersen and −8.14 with placebo (difference, 1.2 points; 95% confidence interval [CI], −3.2 to 5.5; p = 0.97).[10] Other clinical secondary outcomes also did not reach statistical significance. Secondary endpoints of change from baseline at Week 28 in plasma NfL and CSF SOD1 protein were nominally statistically significant. NfL reduction was consistently observed for all subgroups based on sex, disease duration since symptom onset, site of onset, and riluzole/edaravone use. After completion of Study 1, patients had the option to enroll in an open-label extension study. A total of 95 participants (88%) entered the open-label extension. At an interim analysis at 52 weeks, reductions in NfL were seen in patients previously receiving placebo who initiated tofersen in the open-label extension study, similar to the reductions seen in patients treated with tofersen in Study 1. Specifically, 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% CI, 0.4 to 6.7); non–multiplicity-adjusted differences favoring early-start tofersen were seen for other end points. Lumbar puncture–related adverse events were common. Neurologic serious adverse events occurred in 7% of tofersen recipients. Earlier initiation of tofersen compared to placebo/delayed initiation of tofersen 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 tofersen 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.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Qalsody is an antisense oligonucleotide indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene.[1] This indication is approved under accelerated approval based on reduction in plasma neurofilament light chain observed in patients treated with Qalsody. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

References

1. Qalsody [Prescribing Information]. Cambridge, MA: Biogen MA Inc.; April 2023.
2. Brooks BR, Miller RG, Swash M, Munsat TL; World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2000;1:293–299.
3. de Carvalho M, Dengler R, Eisen A, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol 2008; 119:497–503.
4. Geevasinga N, Menon P, Scherman DB, Simon N, Yiannikas C, Henderson RD, Kiernan MC, and Vucic S. Diagnostic criteria in amyotrophic lateral sclerosis: A multicenter prospective study. Neurology. 2016 Aug 16; 87(7): 684-90.
5. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. J Neurol Sci. 1999; 169(1): 13–21.
6. Castrillo-Viguera C, Grasso DL, Simpson E, Shefner J, Cudkowicz ME. Clinical significance in the change of decline in ALSFRS-R. Amyotroph Lateral Scler. 2010;11(1-2):178-80.

7. Subcommittee on Motor Neuron Diseases of World Federation of Neurology Research Group on Neuromuscular Diseases, El Escorial "Clinical Limits of ALS" Workshop Contributors. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. J Neurol Sci 1994; 124: 96–107.
8. National Institute of Neurological Disorders and Stroke. Amyotrophic Lateral Sclerosis (ALS) Fact Sheet. Retrieved from: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Amyotrophic-Lateral-Sclerosis-ALS-Fact-Sheet. Accessed May 9, 2023.
9. Food and Drug Administration. Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee- FDA Briefing Document. March 22, 2023. https://www.fda.gov/media/166326/download. Accessed May 8, 2023.
10. Miller TM, Cudkowicz ME, Genge A, Shaw PJ, Sobue G, Bucelli RC, Chiò A, Van Damme P, Ludolph AC, Glass JD, Andrews JA, Babu S, Benatar M, McDermott CJ, Cochrane T, Chary S, Chew S, Zhu H, Wu F, Nestorov I, Graham D, Sun P, McNeill M, Fanning L, Ferguson TA, Fradette S; VALOR and OLE Working Group. Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. N Engl J Med. 2022 Sep 22;387(12):1099-1110. doi: 10.1056/NEJMoa2204705. PMID: 36129998.

Policy History/Revision Information

Date	Summary of Changes
10/01/2023	**Coverage Rationale** • Removed reference link to the Medical Benefit Drug Policy titled *Review at Launch for New to Market Medications* **Applicable Codes** • Updated list of HCPCS codes to reflect quarterly edits; replaced C9399 with C9157 **Supporting Information** • Archived previous policy version 2023D00123A

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.